GLASS' OFFICE GYNECOLOGY

SEVENTH EDITION

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To Jessica, Rachael, Natalie, Matthew, and Ester who are the loves and lights of my life's journey.

–Michèle G. Curtis, MD, MPH, MML

To Norma, my mother*, for her eternal presence in my life, to Luis,* my husband*, for his support and encouragement, and to Martin,* my son*, happiness and awe every day.*

–Silvia T. Linares, MD

To Borys, my best friend and a true supporter of women. A life without you would be no life at all.

–Leah Antoniewicz, MD

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Preface

Clinical knowledge is estimated to double every 18 to 24 months and although this may appear to preclude the use of written textbooks, knowledge alone does not signify changes in clinical approaches, evaluations, or treatments. In addition, trying to piecemeal knowledge facts together to form a coherent story is not as effective as a collective summary of what is currently known, with the caveat that some things may have changed since the writing, editing, and final publication of the text.

As practitioners, it is abundantly clear that the role of technology in our practices is an ever expanding one with promises of incredible success, breakthroughs, and truly individualized medical care. At times, the breathtaking pace of advances in molecular "–omics," nanotechnology, computer modeling, data mining, and the diminishing size of diagnostic and surgical instruments is enough to make one feel almost obsolete. The appeal of these approaches lies in their underlying premise to get to the true root cause of illness and disease—a confirmation of the reductionistic approach that Western medicine is founded upon. It is enticing to think that if we could just know the exact genetic or proteomics trigger that has started the cascade of events leading to our patient's cancer, we could truly cure them.

But this approach alone is insufficient because it promotes such myopic foci that the issues of context get lost—the context of the patient's life, emotions, relationships, thought patterns, and value systems, all of which are integrated and interrelated in the creation of what is called health. Dr. David Lowe, a mentor of mine, once told me that health is a result of three things: who we are (genetics), where we live (environment), and how we live (lifestyle, daily living decisions). From this viewpoint, one is able to see the interaction of the macroenvironment outside of us with the scientifically seductive microenvironment that lies within us. In my opinion, it is this approach that will allow for the perfect marriage of public health with medical care and hopefully, will result in better health for all. One area with expanding awareness of the interdependent nature of macro and micro effects in women's health is in the fetal origins of disease and epigenetics, where effects may be traced back several generations not just one.

The practice of medical care is a subset of health care overall and the best practitioners; that is, the ones who can truly help their patients optimize their health, understand this, and seek to know more than just a litany of facts related to diagnosis and treatment alone. It is in knowing our patients, and the matrices of their lives both externally and internally, that we are best able to help them maintain their health or optimize it. The human touch we speak of embodies intuition, experience, empathy and compassion, and a willingness to develop a variety of communication skills and approaches so that patients truly know that their provider is listening and that they care. It is the true art of medicine and I believe that its value in impacting our patients' well-being is increasingly underappreciated and undervalued. If it truly has no significant role to play, then it is quite plausible that medical providers will simply become technicians with computers, assays, and technology taking on the role of "clinician."

As a physician who cares for and about a segment of patients that comprises a little over half of the world's population (women and girls), the importance of accurately assessing their health concerns and needs while getting to know them as the individuals they are is brought home in every patient encounter. The title of this book is *Office Gynecology*, but its contents reflect more than just selected gynecologic conditions. The chapters mirror the common issues seen by women's health providers every day and so the scope of this book includes more than just conditions that occur between the belly button and the knees. As we learn more about the interactions between the mind, body, and environment, there is no doubt that future topics we can only begin to imagine now will someday become almost fundamental chapters for textbooks such as this.

Acknowledgments

Identifying willing and expert authors to compose reviews of the issues and conditions we see in the practice of office gynecology is no easy feat—and that is only the first step in the process of producing a textbook. To the authors who did agree to participate—and even those who did not—in this project, I extend my sincere thanks and appreciation for doing so, or at least, considering it. Editing a book that seems to be exponentially increasing its chapter offerings with each edition is a herculean task—especially because it is done in the context of busy daily lives, professional and personal challenges and obligations, and the oh-so-human desire to just relax after a long day or week in lieu of engaging a text with critical and analytical thinking skills. This textbook would not have been possible without the incredible dedication and efforts of my fellow editors, particularly Dr. Leah Antoniewicz and Dr. Silvia T. Linares. They are amazing women as well as fabulous physicians. Then, there is the poor soul who receives the edited chapters, replete with highlights, markups, and ever changing references and tables and who then has to put it all together for the publisher. In this case, it was a woman with a great deal of patience and a strong sense of humor: Franny Murphy. Without her keeping us all on track and being able to learn our collectively different editing styles and approaches, this textbook would have not been possible.

This marks the third edition of *Glass' Office Gynecology* where I have served as the lead editor. It will also be my last. It is amazing to me how many life events can occur over the course of three editions, but through it all, the love of family remains and strengthens. I have reached the midway point of life and am currently reflecting on what it is I want to do for the next 20 years or so of my working life. I have told my friends and colleagues that if you only edit a book once, it may mean you did not do so well at it. If you edit it twice, you did do a good job the first time as reflected in the invitation to do it again. If you do it three times, you might want to consider an evaluation for a *DSM-5* diagnosis of some sort. For me, four times would be grounds for commitment and besides, it is time to do new things and develop new skill sets and perspectives. I hope these editions have been helpful to all of those providers who work to help women and their children and families. I hope there are further editions to come as well that will never lose sight of the fact that practicing medicine at both the macro and micro levels truly creates health care outcomes that are greater than just the sum of their component parts.

Michèle G. Curtis, MD, MPH, MML

SECTION

Common Gynecologic Conditions

CHAPTER 1

Contraception

Leah Antoniewicz

The use of contraception started since humans were able to associate coitus and pregnancy. Documents from 1850 BCE (the Kahun papyrus) describe several methods to create a hostile environment or a physical barrier for sperm. The Romans during the second century AD developed a spermicidal barrier using wool and an acidic vegetable mix.[1]

The voluntary control of fertility is of paramount importance to modern society and a central role of health care providers. To ensure suatainable development, countries need to plan population growth. More importantly, empowering women to control their reproductive capacity allows them to reach individual, familial, and societal goals, contributing to personal and collective well-being. Having freedom to decide over their sex life, procreation, and lifestyle is a fundamental right of women and is critical to achieving gender equality and women's autonomy. Unfortunately, depriving women of their sexual and reproductive rights is the main method used in many societies around the world to keep them from achieving their right place in society.

In the United States, 50% of all pregnancies are unintended, and approximately half of these end in abortion.[2] Of these, 50% of unintended pregnancies occurred despite the use of contraception. Although decreasing, adolescents have the highest unintended pregnancy rate. Disappointingly, the rate has increased for low-income and less educated women.[3]

Regulating fertility improves maternal and neonatal outcomes.[4] In developing countries, family planning programs prevent an estimated 187 million unintended pregnancies, including 60 million unplanned births, 105 million abortions, and averts an estimated 2.7 million infant deaths and 215,000 pregnancy-related deaths.[4] For a comparison of birth-related and method-related deaths, see Figure 1.1.[5]

The introduction of birth control methods that are easier to use and more effective provides women the opportunity to choose the one that better fits their personal preferences, health needs, and lifestyles. Contraceptives can be mechanical, hormonal, and behavioral. No method is 100% effective nor does any of them guarantee a perfect fit for every woman's needs. Each presents its own benefits, risks, and side effects. The decision of which method to use belongs to the patient. The role of the health care provider is to empower the patient by offering suggestions according to her health history, her personal lifestyle, psychological and social factors, the methods' correct use and side effects, and of course any contraindication that may apply to her case.

OVERVIEW OF CONTRACEPTION

Contraceptives are either hormonal or nonhormonal. Contraceptives can be taken orally, be injected, or be slowly released through direct contact with the body. Hormonal contraceptives use estrogen and/or progesterone and have several mechanisms of action. Estrogen prevents formation of the dominant follicle, potentiates progesterone, and stabilizes the endometrium. Ethynil estradiol (EE) is almost exclusively used as the estrogen component in hormonal contraceptives and is usually the component that is relatively or strongly contraindicated in some patients. Progesterone prevents ovulation, thickens cervical mucus, suppresses endometrial growth, and perhaps alters secretions and peristalsis of the fallopian tubes. The progestational compounds are varied, as are their side effect profiles. In the last two

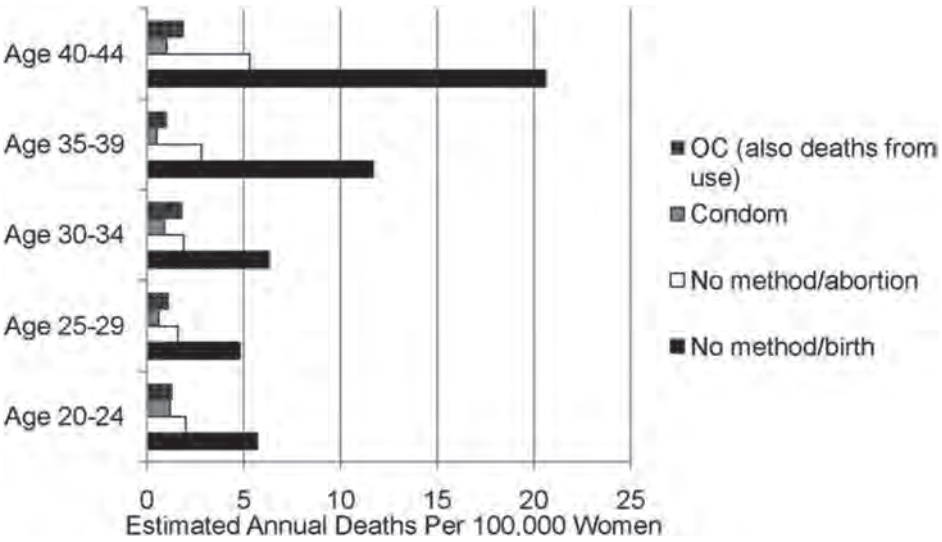

FIGURE 1.1 Estimated annual deaths per 100,000 women according to contraceptive use. (From Maguire K, Westhoff C. The state of hormonal contraception today: established and emerging noncontraceptive health benefits. *Am J Obstet Gynecol*. 2011;205:S4–S8.)

TABLE 1.1 Percentage of Women With Unintended Pregnancy During First Year of Typical Use and First Year of Perfect Use of Contraception and Percentage Continuing Use at End of First Year, United States

	% of Women Experiencing Unintended Pregnancy Within First Year of Use		% of Women Continuing Use at 1 Year[c]
Method (1)	**Typical Use[a] (2)**	**Perfect Use[b] (3)**	**(4)**
Chance[d]	85	85	
Spermicides[e]	26	6	40
Periodic abstinence	25		63
Diaphragm[f]	20	6	56
Withdrawal	19	4	
Condom (male)[g]	14	3	61
Pill	8		71
Ring	8	0.3	
Patch	8	0.3	
IUD			
Copper T380A	0.8	0.6	78
LNG 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Levonorgestrel			
Implants (Implanon, Nexplanon)	0.4	0.4	88
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

[a]Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
[b]Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
[c]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.
[d]The percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
[e]Foams, creams, gels, vaginal suppositories, and vaginal film
[f]With spermicidal cream or jelly
[g]Without spermicides
Adapted from Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, et al, eds. *Update to Contraceptive Technology*. 19th ed. New York: Ardent Media, Inc; 2007.

TABLE 1.2 Strong Contraindications to Combined Hormonal Contraceptive Use

- Thrombogenic disorders (factor V Leiden, prothrombin mutations; protein C, S, or antithrombin deficiency)
- History of or current venous thromboembolism without anticoagulation
- Cerebral vascular or coronary artery disease
- Known or suspected estrogen-dependent neoplasm
- Abnormal uterine bleeding of unknown etiology
- Liver disease, including hepatic adenomas, carcinomas, benign liver tumors or acute infections (mononucleosis, hepatitis)
- Known or suspected pregnancy
- Conditions that increase the risk of myocardial infarction (smoker at age 35 years or younger, diabetes with complications)
- Migraine with aura
- Systemic lupus with complications or antiphospholipid antibodies
- In patients with conditions that predispose to hyperkalemia (renal insufficiency, adrenal insufficiency, hepatic dysfunction), YAZ and Yasmin should be used with caution because they contain drospirenone, an aldosterone antagonist.

decades, we have seen a decrease in both side effects and vascular complications of hormonal contraception as a result of lower doses of estrogen and progestins. In general, the estrogen-related contraindications are for those patients with cardiovascular disease, with thromboembolic disease or risks, and with liver disease. The most common contraindication for progestin-only methods is unwillingness or inability to accept irregular bleeding, including amenorrhea. With the exception of the copper-releasing intrauterine device (IUD) and sterilization, nonhormonal methods are far less cost-effective. This chapter begins with considerations of certain medical conditions at certain times of the reproductive spectrum. It continues with a detailed discussion of various reversible methods, starting with the most effective, followed by a discussion of permanent methods.

Contraception Concerns With Selected Medical Conditions and Special Populations

When considering that the hormone levels in pregnancy are far higher than those produced by combination (estrogen-progestin) hormonal contraceptives (oral contraceptives [OCs], the patch and the ring), there

TABLE 1.3 Relative Contraindications to Combined Hormal Contraceptive Use

- Controlled hypertension
- Multiple risk factors for cardiovascular disease (diabetes, obesity, hypertension, lupus, hypertriglyceridemia)
- Medicines that induce liver enzyme metabolism and decrease contraceptive efficacy
- History of cholestatic jaundice during pregnancy or active gallbladder disease
- Breast-feeding

TABLE 1.4 Strong Contraindications to Progestin-Only Methods

- Known or suspected progesterone-dependent neoplasm
- Known or suspected pregnancy
- Unwillingness/inability to have irregular bleeding or amenorrhea
- For both formulations of depo medroxyprogesterone acetate
  - Fragility fracture
  - Desire for pregnancy within a year
  - Current use of aminoglutethimide

are few absolute contraindications to combination hormone contraceptives (CHCs). Progestin-only methods and nonhormonal methods, such as the copper IUD, are a good option for women with relative or strong contraindications to estrogen. Depending on the patient's desires, sterilization may be the best option. For a complete list of strong and relative contraindications to CHCs (including the patch and ring), see Tables 1.1 and 1.2. Other disorders that are relative contraindications to the use of progestin-only methods are listed in Tables 1.3, 1.4, and 1.5.

Adolescents

Establishing confidentiality is of paramount importance with adolescents. Clinicians need to be familiar with how teens think and feel about sex and birth control, what their beliefs and emotions are, and how individual teens may make choices based on their lifestyles and social and affective circumstances. Oral CHCs and condoms are the most commonly used method by this age group, and concomitant use should be encouraged to protect against both pregnancy and sexually transmitted diseases (STDs). Long-acting reversible contraceptive (LARC) methods (IUDs and implants) are safe and effective and should be considered first line.[4]

Postpartum

Because of the higher risk of thrombosis after parturition, it is prudent to delay CHCs until 4 weeks postpartum. IUDs can be inserted immediately postpartum or anytime thereafter. The advantages to immediate insertion are obvious but there is evidence regarding increased expulsion

TABLE 1.5 Relative Contraindications to Progestin-Only Methods

- Controlled hypertension
- Multiple risk factors for cardiovascular disease (diabetes, obesity, hypertension, lupus, hypertriglyceridemia)
- Medicines that induce liver enzyme metabolism and decrease contraceptive efficacy
- History of cholestatic jaundice during pregnancy or active gallbladder disease
- Breast-feeding

rates for this approach, with the lowest expulsion rates occurring immediately postpartum.[5–7] Progestin-only pills can be given at 3 weeks in nonlactating women. Rarely, depo medroxyprogesterone acetate (DMPA) can cause metrorrhagia if given before 6 weeks postpartum but is otherwise safe to give at anytime in nonlactating women.

Lactation

Many authorities recommend nonhormonal or at least delaying hormonal contraceptives until 6 weeks postpartum. Because withdrawal of progesterone with delivery of the placenta is a lactogenic trigger and because estrogen has negative feedback on prolactin, it makes theoretical sense that these hormones could negatively impact lactation. Additionally, there are concerns of hormone transfer to the infant depending on the formulation. A Cochrane review found existing randomized controlled trials are insufficient to establish an effect of hormonal contraception on milk quality and quantity.[7] Therefore, if lactational amenorrhea or a nonhormonal option is not possible, a progesterone-containing contraceptive is recommended at 6 weeks postpartum. Earlier administration should be considered for certain situations.

Women Older Than Age 35 Years

Healthy women older than age 35 years who do not smoke and are not obese can safely take CHCs.

Perimenopause

The need for safe and effective contraceptive methods remains great in the perimenopausal period as evidenced by the high unintended pregnancy rate in this age group, often from a misconception that they do not think they are fertile. In fact, the pregnancy termination rate in women 40 to 50 years of age is exceeded only by those women younger than 15 years of age.[2]

The transition period of changing hormone patterns, or perimenopausal state, begins about 5 to 10 years before the actual menopause. Characteristics of the perimenopause are irregular cycles; changes in both the volume and the duration of bleeding; and for approximately half the women, the onset of variable vasomotor symptoms. The perimenopausal period is characterized by an increased incidence of anovulatory cycles, resulting in an unopposed estrogen state. This predisposes to dysfunctional uterine bleeding, possible endometrial hyperplasia, and a poorly documented, but frequently observed, accelerated growth of uterine myomata. CHC should be the method of choice for nonsmoking, nonobese women to regulate menstrual periods, provide contraception, control vasomotor symptoms, protect bone health, and reduce the risk of endometrial and ovarian cancers. These women often do well on the lowest estrogen dose of 20 mcg. Because there is no good test to confirm menopause, she can continue combined hormonal contraception until the age of 51 to 55 years, unless there is a change in her health status.

Cerebrovascular Disease

CHCs are contraindicated in the presence of cerebrovascular disease. They also increase the risk for stroke in women with other underlying risk factors.[8]

Migraine and Headache

Patients with a history of migraine headaches should use CHCs cautiously. Some patients will note an improvement, whereas some will notice no change; however, approximately 50% of patients will notice a worsening of their condition, especially during the hormone-free interval. One commonly accepted contraindication to the use of CHCs is a history of classic migraine (migraine with focal neurologic symptoms or aura lasting 5 to 60 minutes) due to an increased potential for stroke. It should be noted that women with a history of migraines have a two- to three-fold increased risk of ischemic stroke, regardless of CHC use.[8]

Seizure Disorder

CHCs have no impact on the pattern or frequency of seizures. However, some anticonvulsants can decrease serum concentrations of estrogen and thus may increase the likelihood of intermenstrual bleeding.[9] An increase in ovulation or accidental pregnancy has never been shown. Although there is no published data to support this, some clinicians start with a 50 mcg EE formulation. Starting with at least 30 to 35 mcg of EE does seem reasonable. If a woman has been started on a 30 mcg EE formulation and develops intermenstrual bleeding, switching to a 50 mcg EE pill may be helpful. Anticonvulsants that do not appear to decrease serum estrogen levels when used concurrently with a CHC include levetiracetam, valproic acid, ethosuximide, and zonisamide.[9] Gabapentin, lamotrigine, and tiagabine do not lower estrogen levels either but they have been studied at subclinical doses.[8]

Cardiovascular Disease

Almost all excess mortality in combined OC users is due to cardiovascular disease. Most of these deaths are due to myocardial infarction (MI). The cardiovascular disease risk is most prevalent in women older than 35 years of age who smoke.[12,13]

Venous Thromboembolism

Although not a major cause of morbidity and mortality, venous thrombotic disease and pulmonary emboli are

known side effects of CHC use. The dose of EE and type of progesterone influence this risk (desogestrel [DSG] and gestodene [GSD] are associated with a two-fold greater risk). Package labeling for certain progestin-only contraceptives list thromboembolism as a contraindication, but this is no supporting evidence for this claim.[13] The transdermal patch, however, did increase venous thromboembolism (VTE) by two-fold in one cohort study.[13] Coagulopathy screening is not cost-effective unless there is personal or family history. Unexplained VTE, hypercoagulable states, and VTE associated with pregnancy or exogenous estrogen are contraindications to combination OCs unless the patient is anticoagulated. Other risk factors for VTE should be considered.[2]

Obesity

Obesity (body mass index [BMI] greater than 30 kg/m^2), and even being overweight (BMI greater than 25 kg/m^2) are independent risk factors for VTE. In obese women ages 35 years or younger, CHC use is appropriate, although there is some evidence that with overweight or obese patients, the efficacy is less than with women with normal BMI.[9] Similarly, women weighing 90 kg or more had significantly higher failure rates with the transdermal patch. Obese women should be counseled regarding this possibility. The levonorgestrel IUD is an excellent choice because it circumvents potential problems related to EE and provides endometrial protection and stabilization.[8]

Hypertension

If a patient has hypertension, it should be controlled (to less than 140/90 mm Hg) prior to beginning combination OCs because they have the potential to aggravate this condition.[12,13]

Increases in blood pressure have been reported in women taking OCs, and follow-up evaluation of blood pressure in such patients is advised. If the blood pressure is controlled and no vascular disease is present, CHCs are not contraindicated. A history of pregnancy-induced hypertension does not preclude the use of CHCs as long as the blood pressure returns to normal postpartum.[13]

Dyslipidemia

Women younger than age 35 years, in the absence of uncontrolled hypertension, diabetes, or other OC contraindications, may consider CHC use. In general, estrogen decreases low-density lipoprotein (LDL), increases high-density lipoprotein (HDL), and increases triglycerides, but does not increase atherosclerosis.[13] This effect is seen with the transdermal patch and the vaginal ring. An OC with a less-androgenic progestin increases HDL more and triglycerides less. If a woman's triglycerides are above 350 mg/dL or in patients with familial hypertriglyceridemia, CHCs should be avoided because they may precipitate pancreatitis and/or adversely affect the patient's risk for cardiovascular disease.

Mitral Valve Prolapse

In general, CHCs can be safely used by women with mitral valve prolapse (MVP) who are symptom free. Use should be limited to MVP patients with an echocardiographic-confirmed diagnosis but without mitral regurgitation. A history of thrombotic complications would require another contraceptive method. Long-acting progestins such as injection or implants are safe to use and may provide increased fibrinolytic activity.

Diabetes

Young diabetic women who are free of retinopathy, nephropathy, hypertension, or other complicating vascular disease(s) are appropriate candidates for low-dose contraceptives. The progestin component of CHCs is believed to increase insulin resistance, although this has not had a verified clinical effect.[8] Women with a history of gestational diabetes during their last pregnancy can safely take low-dose CHCs. The incidence of frank diabetes developing within 3 years of pregnancy is no higher in women taking low doses of CHC than in those using nonhormonal contraceptive methods.[10]

Systemic Lupus Erythematosus

CHCs can be given to women with mild lupus (no vascular disease or nephritis) and no antiphospholipid antibodies.[12]

Sickle Cell Disease

Internationally, recommendations for women with sickle cell disease and CHC use vary widely. DMPA is an excellent choice, as it reduces painful crises.[8] In the United States, many clinicians think that the risks of pregnancy far outweigh the risks associated with CHC use in women with sickle cell disease. Thus, CHC are often prescribed for this population.[11,12]

Oral Contraceptives and Cancer

Breast Cancer

Fear of developing breast cancer has been a deterrent to the use of both hormonal contraceptives and hormone replacement therapy. The issue has been one of major debate for a number of years, and it is still unresolved.[13–15] Early studies suggested a slight association between OC use and breast cancers in *BRCA1/BRCA2* carriers. Results of the Women's Contraceptive and Reproductive Experiences (CARE)[15a] study showed no association between CHCs and DMPA and breast cancer in patients with benign breast disease or a family history

of breast cancer, including *BRCA1/BRCA2* mutations. Some recent studies have presented nonconclusive results that suggest a slightly increased risk for mutation carriers. Despite the failure to prove any decisive association between CHC use and breast cancer, the hypothesis is biologically plausible. Even a slight but hard to prove risk increase could be highly significant given the high incidence of breast cancer. Therefore, the controversy is likely to continue until larger longitudinal studies show more definitive results.

Cervical Cancer

OCs alone do not increase the risk of cervical cancer. However, there is strong evidence that recent use of CHC is associated with increased risk of human papillomavirus (HPV) infection independent of sexual behavior and cervical abnormalities.[16] Among HPV-infected women, those who used OCs for 5 to 9 years have approximately three times the incidence of invasive cancer, and those who used them for 10 years or longer have approximately four times the risk.[17] On the other hand, such association is not observed with progestin-only contraceptives (i.e., DMPA). The mechanism is probably related to CHC affecting host response, making her less likely to clear HPV infection rather than increasing the risk of HPV acquisition.[18]

Endometrial Cancer

Numerous studies have shown a decrease in the risk of endometrial cancer of about 50% in combination oral contraceptives (COC) users. The protective effect is greater with longer duration of CHC use and higher progestogen potency and persists for more than 20 years after cessation of the CHC. Because endometrial cancer is thought to be caused by unopposed estrogen stimulation, progestogen-containing contraceptives could protect against endometrial cancer. The reduction of inflammation in the endometrium produced by CHCs may be the cellular mechanism behind the lower incidence of endometrial carcinoma in CHC users.[19] Although CHCs can effectively reduce endometrial hyperplasia, it should be used only under certain circumstances in patients with or after endometrial cancer.[20]

Ovarian Cancer

Use of CHCs is associated with up to a 46% reduced risk of ovarian cancer compared with never use. As with endometrial cancer, protection from ovarian cancer may persist for up to 20 years after discontinuation of COCs.[17,19] The blockade of ovulation, follicular rupture, and ovarian production of steroids may explain the lesser incidence of ovarian cancer among CHC users. The degree of protection is directly related to the duration of use, with the most significant reduction seen in women using them for more than 8 years. A 20% reduction is seen for every 5 years of use, but some protection is conferred with as little as 3 to 6 months of use. There does not appear to be any diminution in protection with the use of low-dose combination OCs.[20] Furthermore, CHCs appear to reduce ovarian cancer for carriers of *BRCA1/BRCA2* mutations.[21]

Oral Contraceptives and Surgery

Estrogen-containing OCs significantly increase the likelihood of both idiopathic and postoperative venous thrombosis and pulmonary embolism. Although these effects were most marked with early, high estrogen content OCs, there is still risk with present-day preparations containing 30 to 50 mg estrogen. More selective choice of CHC users, reduced estrogen doses, and better surveillance of users appear to have diminished the risk of thromboembolic disease with CHC use. But unfortunately, there are no sure predictors of thromboembolic disease. Because the thrombotic effects of CHCs stop by 4 weeks after termination, it is recommended that CHC use be interrupted one cycle before elective surgery, but the risk of thrombosis should be balanced against the risk of pregnancy. If prolonged immobilization is expected, they should be discontinued. Heparin prophylaxis should be considered if they are continued.[22]

LONG-ACTING REVERSIBLE CONTRACEPTIVE METHODS

Contributing to the many reasons there is a high unintended pregnancy rate in the United States is the popular use of less effective methods (CHCs and condoms), which have high discontinuation rates. LARC methods (IUDs and implants) could help mitigate these factors, with very few contraindications. Several studies have shown that LARC methods reduced repeat adolescent pregnancy and repeat abortions.[3] In fact, expanding access to LARC has been declared a national priority by the Institute of Medicine.[23]

Although these contraceptive methods may have high cost initially, they have multiple advantages over other methods: They are not user-dependent, are highly cost-effective, have high continuation rates, and satisfaction and effectiveness are higher than other methods. They do not require additional visits for resupply or additional funding; furthermore, they offer a rapid return to fertility once discontinued.

Practitioners can increase LARC use in several ways: First, counseling all patients on these methods, including nulliparous and adolescent women[24,25]; second, avoiding unnecessary delays, such as screening for gonorrhea, chlamydia, or cervical cancer; third, avoiding waits for a follow-up visit after pregnancy (abortion, miscarriages, or term), especially in patients at risk for not returning.[25,26]

Intrauterine Devices

IUDs are highly effective with a pregnancy rate of less than 1% after 1 year. All IUDs are spermicidal by interfering with sperm transport and creating a sterile inflammatory environment in the uterus. Prefertilization properties constitute the primary mechanism of action, although the loss of the fertilized ovum may occur before implantation.[27] As previously stated, IUDs do not increase the rate of pelvic inflammatory disease or tubal occlusion. Cervical cancer and STI screening can be done just before insertion if indicated. If treatment for infection is necessary, the IUD should not be removed.[27] Return to fertility is immediate when removed.

Copper Intrauterine Devices

In addition to the mechanism above, copper is directly toxic to sperm, increasing its effectiveness. The TCu-380A (ParaGard) is currently approved for 10-year placement, but may be effective for 12 years. Because of this, it has the highest efficacy with the lowest cost. It is a good option for women who cannot or do not want to take hormones. It may also be used for emergency contraception. The copper IUD may cause dysmenorrhea and a 30 to 50% increase in menstrual flow, which can be mitigated with nonsteroidal anti-inflammatory drugs (NSAIDs). The discontinuation rates due to these two side effects is 12% so the patient should be asked ahead of time if dysmenorrhea and increase in menstrual flow would be acceptable.[28] Over time, copper IUDs are associated with stable ovulatory bleeding patterns, but prolonged bleeding is common in the first few months.[29] The 10-year cumulative failure rate is 2.1 to 2.8% (Fig. 1.2).

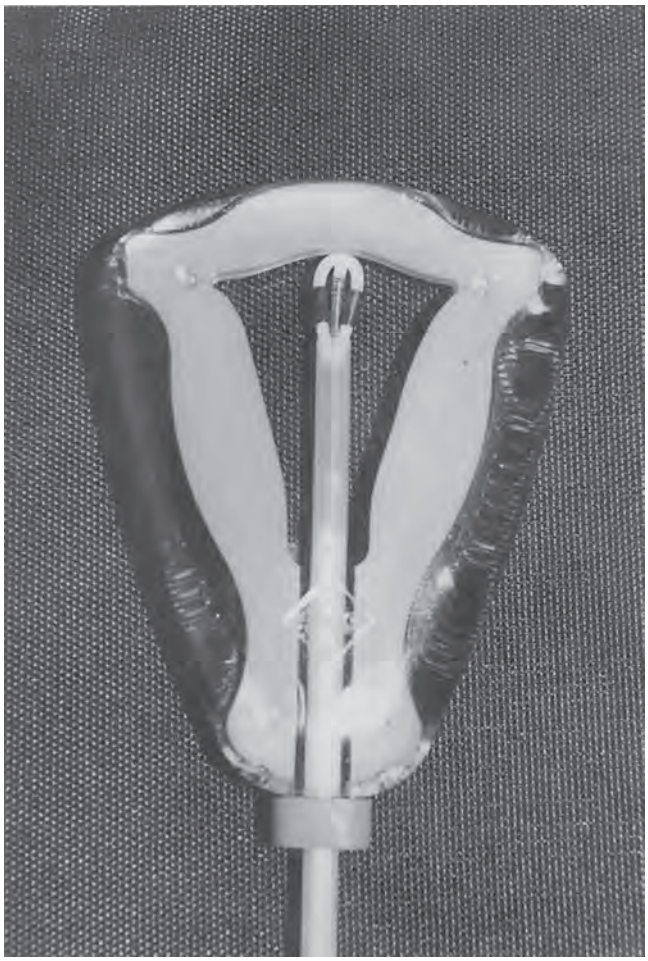

FIGURE 1.2 Copper IUD (ParaGard) readied for placement.

Levonorgestrel-Releasing Intrauterine Device

The levonorgestrel (LNG)-releasing IUD (Mirena) releases 20 mcg LNG daily. It inhibits sperm transport, thickens cervical mucus, partially inhibits ovulation, and causes reversible atrophy of the lining. These actions reduce menstrual flow by 70% at 6 months and by 90% at 12 months.[30] Amenorrhea is seen in 30% of users by 2 years of use.[31–33] The Mirena also improves dysmenorrhea so its use may be preferable in women experiencing heavy or painful periods. The Mirena IUD has been approved for 5 years of use but may be effective for up to 7 years. Two large clinical trials in Finland and Sweden with more than 1600 women and 45,000 cycles of use have demonstrated cumulative 5-year pregnancy rates of less than 0.7 per 100 women.[34]

Although irregular spotting or bleeding may occur in the first few months, this usually diminishes over time. The majority of women who continue to have cyclical menses with the LNG IUD have ovulatory progesterone levels, but only 58% of these women have normal growth and rupture of ovarian follicles on ultrasound exam. Of the women who do not have cyclical menses, 29% have growth and rupture of follicles.[35] It is not surprising then that women using the LNG IUD can develop large (greater than 3 cm) ovarian cysts. In one study, all these cysts spontaneously resolved over a 4-month period, and it is believed the formation of these cysts is of limited significance.[36] These findings are similar to what has been seen with the subdermal LNG implants.[37] As eluded to earlier, there are a host of noncontraceptive benefits with the LNG IUD. In addition to treatment for menorrhagia and dysmenorrhea, it can be used to protect the endometrium from effects of unopposed estrogen.

Complications Associated With IUD Use

The risk of pelvic inflammatory disease (PID) is about 1/1000 and occurs in the first 20 days postinsertion. Women at risk are those with bacterial vaginosis and cervicitis. These infections should be treated with the IUD in place. Uterine perforation is also 1/1000 and is more common with immobile or anteverted or retroverted uteri, lactating women, and inexperienced inserters.

LNG IUD expulsion is more common in younger women, women who have not had children, and when an IUD is inserted immediately after childbirth or abortion. There is a higher risk of expulsion for women who have never given birth.[38] LNG IUD expulsion rate is about 3% when used exclusively for contraception and 9 to 14% when used to control bleeding.[39,40] IUDs decrease the rate of ectopic pregnancy compared with no contraception. However, if pregnancy occurs, the risk of an ectopic pregnancy is increased and the patient should be evaluated immediately.

When pregnancy is diagnosed in the presence of an IUD, the location of the pregnancy (intra- or extrauterine) should be determined and the device removed as soon as possible in the first trimester. Septic abortion is greatly increased when pregnancy is complicated by IUD. Women who become pregnant with an IUD in place have a 50% increased rate of spontaneous abortion. After removal of the IUD, the spontaneous abortion rate decreases to about 30%. If it cannot be removed or she chooses not to have it removed, she should be counseled that in addition to the increased spontaneous abortion rate, the risk of preterm labor, delivery, and sepsis are increased. She can be reassured that there is no increase in congenital anomalies.

Removal of an IUD in an infected, pregnant uterus should be accomplished only after intravenous antibiotic blood levels have been achieved. The removal of the IUD should be done in a location where emergency measures are available, in case septic shock ensues.

The IUD can be inserted safely at any time after abortion or delivery. There is a higher rate of expulsion for the delayed postpartum insertions, although it can be prevented with high fundal placement. Additionally, the rate of expulsion is lower for immediate postpartum insertions (within 10 minutes of placental delivery) than for delayed insertions (within 48 hours of delivery).[22] Insertion of the IUD during the period of lactational amenorrhea has the advantage of significantly decreasing the spotting problem often encountered during the first cycle after insertion. Directions for placement of the copper and progesterone IUDs are found in Appendices 1.A and 1.B.

The patient should check for the IUD string monthly, and the practitioner should check for it at the time of gynecologic examination. If twirling a cytobrush in the cervical canal does not bring the strings into view, an ultrasound should be done to confirm intrauterine location. If the ultrasound does not show it, a flat plate abdominal radiograph can be taken, with an abdominal series to triangulate the location. If the IUD is intra-abdominal/extrauterine, it must be physically retrieved. An intra-abdominal IUD can cause serious problems, including bowel obstruction or perforation. Removal should be done as soon as possible after the diagnosis is made. Copper IUDs, in particular, elicit a strong inflammatory response that may make laparoscopic removal quite difficult. Perforation of the uterus usually occurs at the time of insertion, so it is important to identify the strings a few weeks afterward.

To remove an IUD, the strings are grasped with either a ring forceps or uterine dressing forceps and firm traction is exerted. If the string(s) cannot be seen, a cytobrush in the endocervical canal may help in extracting them. If ultrasound confirms intrauterine location, a paracervical block can be given before using alligator forceps or other instruments in the uterus. Visualization of the IUD with sonography or hysteroscopy may be necessary to facilitate removal.

Implants

Implanon, a single-rod subdermal implant the size of a matchstick, releases 68 mg of etonogestrel (metabolite of DSG) over 3 years. It releases about 40 mcg/day by the end of the first year and 25–30 mcg/day at the end of the third year. It is effective within 24 hours of insertion and prevents pregnancy by immediate thickening of cervical mucus, inhibition of ovulation, and endometrial atrophy. The Pearl index is less than 0.07 pregnancies per 100 woman-years if it is implanted in the *first 5 days* of the menstrual cycle.[38]

Implanon is convenient, has a high continuation rate, is rapidly reversible, does not affect bone density, and is easy to remove. Of note, the U.S. Food and Drug Administration (FDA) requires training to place or remove Implanon, and the manufacturer will not fill orders for physicians who are not trained. The procedure is very simple, requiring local anesthesia and a 2- to 3-mm incision between the bicep and tricep of the nondominant arm so that the distal end of the implant is 8- to 10-cm proximal to the medial epicondyle.

Side effects due to atrophy (irregular bleeding) were the most common reasons for discontinuation according to the package insert (11%). Other side effects such as headache and weight gain occurred in more than 5% of users but were not common reasons for discontinuation. Complications related to insertion and removal are much less common than with Norplant.[39] Implanon is contraindicated in patients being treated with CYP3A-inducing or CYP3A-inhibiting medications.

Jadelle, a two-rod subdermal implant was approved by the FDA for 5 years of use but is not currently marketed in the United States.

ORAL CONTRACEPTION

The development and widespread use of combination hormone contraceptives (CHC) was a major breakthrough in the 20th century. Many observers regard this development as second in importance only to the development and use of broad-spectrum antibiotics.

In choosing a CHC, the optimal formulation will comprise the lowest effective dose with acceptable bleeding profiles and minimal side effects. Certainly, there is a trend in lower estrogen doses, less androgenic progestins, and fewer total days of menstrual bleeding. CHCs impact protein, lipid, and carbohydrate metabolism, but this may not be clinically important. In the United States, CHCs with less than 50 mcg estrogen use EE as the estrogenic component. Lower doses are as effective and have less thrombotic risk and probably less side effects (nausea, breast tenderness, headache, hypertension). Combined hormonal contraceptives can be taken cyclically, by an extended regimen, or continuously.

Most women start CHCs containing 20 to 35 mcg EE. Some of the newer CHC formulations contain fewer placebo days or days with EE only. Some pills contain iron or folate and are chewable. Among the progestins, there are second-generation CHCs, which contain norethindrone (LNG, norgestimate), and third-generation CHCs, which contain DSG or GSD. Drospirenone and dienogest are the newest. Both DSG and norgestimate are less androgenic. The increase in thromboembolism reported in some studies with DSG and GSD may be due to confounding, as there is no biological evidence of this effect.[40] Clinicians can offer several options of CHCs to patients based on their individual characteristics, preference, and tolerance. For example, Yasmin and YAZ are both FDA approved for premenstrual dysphoric disorder (PMDD). These are also a good choice for polycystic ovarian syndrome, hirsuit, or hypertensive patients because drospirenone is antiandrogenic and a diuretic.

Benefits of Oral Contraception

Known benefits of CHC use include the prevention of unwanted and extrauterine pregnancies, reduction in pelvic inflammatory disease, recurrent ovarian cysts, ovulatory pain, premenstrual syndrome, PMDD, and blood loss/iron-deficiency anemia. They also decrease the rate of ovarian, endometrial, and colorectal cancers.[41] They may increase the pleasure of intercourse because it can be spontaneous and without worry of pregnancy. The efficacy of CHCs and other methods is depicted in Table 1.1.

Disadvantages of Oral Contraceptives

Unscheduled bleeding and side effects are a major source of patient noncompliance and discontinuation but tend to resolve after 3 months of use. Therefore, watchful waiting and reassurance is a more logical approach to CHC prescribing than continued switching from one formulation to another. The key to success is an informed patient. Breakthrough bleeding (BTB) is more common in women who smoke and with 20 mcg formulations. Make sure she is taking them regularly because this is the most common reason for BTB. If it persists, rule out pregnancy, infections, drugs that interfere with OCs, and cervical cancer. If the bleeding is just before the placebos, she can stop the pack and start again in 4 to 7 days (depending on the number of placebo pills normally in the pack). If it occurs midcycle, give 7 days of estrogen (EE 2 mg or conjugated estrogen 1.25 mg) while she is taking the OCs.[40] Alternatively, switch to a higher dose pill. Side effects (nausea, headache, breast tenderness, decreased libido) are markedly reduced with pills containing less than 50 mcg estrogen. When side effects do occur, they will usually decline after the first 3 months of OC use. Patients with refractory nausea may try taking the OC immediately after a meal rather than at night on an empty stomach. Changing to a lower dose pill may also help. Additionally, if side effects occur during the placebo pills, consider an extended or continuous cycle regimen.

A Cochrane review assessed 42 trials, including 3 placebo-controlled randomized clinical trials; none of the randomized trials showed a statistically significant difference in weight gain for CHC users compared with the placebo group.[42] Patients need to understand that pills offer no protection from sexually transmitted infections (STIs) and that condoms should be used in nonmonogamous relationships. Other complications include risk of MI, VTE, neoplasia (liver and adenocarcinoma of the cervix), and hypertension (HTN). Prescribe a 3-month supply, but discuss with the patient that monthly trips to the pharmacy may be required.

Clinical Decision Making

Dosing Choices

The World Health Organization (WHO) and FDA recommend using the lowest effective dose.[41] Traditional CHCs contain formulations using EE in combination with various types of progestins for 21 days with 7 days of placebo. Mestranol is used, rarely, and is equivalent to 35 mcg of EE. Clinical choices of a CHC may be based on either the type of progestin agent in the pill or the dose of EE. CHCs with EE may contain 50 mcg (first generation), 40 mcg, 30 mcg, 25 mcg, or 20 mcg. In general, the higher the dose of EE, the better the cycle control, although the type of progestin used in a formulation and the estrogen-progestin ratio may also effect cycle control.[43] In one large open-label study, a triphasic OC with 25 mcg EE and DSG (Cyclessa) was compared with a combination triphasic OC containing 35 mcg EE and norethindrone acetate (NETA). The triphasic combination containing 25 mcg EE and DSG had a significantly lower rate of intermenstrual bleeding and spotting (11%) in comparison to the triphasic combination with 35 mcg EE and NETA. These results may be due to the higher progestational activity of DSG compared with NETA, even though the dose of EE was higher in the NETA combination.[44] In a recent Cochrane review, second- and

third-generation progestins were superior to first-generation progestins for cycle control.[45] Multiphasic pills were created to decrease total hormone levels and side effects with increasing cycle control. So far, this has not been shown to be the case, but many studies were comparing different progestational agents. A recent prospective study in Iran compared LNG in a monophasic and triphasic formulation. There was no difference in side effects, but the triphasic pill was superior for cycle control.[46] Because we do not have enough evidence that triphasic pills have improved bleeding profiles, some experts recommend starting with the cheaper monophasic pills for new users.[47] Biphasic pills have the worst cycle control and are rarely used.[48]

Many newer CHCs also have an extended cycle regimens that have 24 to 28 hormone pills and typically use 20 to 25 mcg of EE. This decreases the chance of ovulation, decreases side effects of endogenous estrogen production, and decreases the days and amount of menstrual flow.[49] Theoretically, use of the additional EE would contribute to the stabilization of bleeding patterns even though the overall dose of EE is low, but in reality, studies have shown increases and decreases in BTB. Extended cycle or continuous CHCs are an option for women with hormone withdrawal symptoms, dysmenorrhea, endometriosis, menorrhagia, or women who simply desire fewer menstrual cycles. With continuous regimens, unscheduled bleeding is seen more frequently but it is reduced over time.

Use of CHCs containing 50 mcg estrogen should be reserved for women requiring additional estrogen to prevent intermenstrual bleeding (e.g., women using drugs that induce hepatic enzymes) or women who have recurring functional ovarian cysts while on OCs containing less than 50 mcg estrogen.

For first-time CHC users, it is best to see them 3 months after initiation of pills to monitor side effects, blood pressure, proper usage, etc.

TABLE 1.6 Drug Interactions With Hormonal Contraceptives

	Category				
Condition	**COC**	**P**	**R**	**CIC**	**Clarifications**
COC, combined oral contraceptives; **P**, combined contraceptive patch; **R**, combined contraceptive vaginal ring; **CIC**, combined injectable contraceptives					
Drug Interactions					
Antiretroviral Therapy					
a) Nucleoside reverse transcriptase inhibitors (NRTIs)	1	1	1	1	Clarification: Antiretroviral drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. Limited data (summarized in Annex 1) suggest potential drug interactions between many antiretroviral drugs (particularly some NNRTIs and ritonavir-boosted protease inhibitors) and hormonal contraceptives. These interactions may alter the safety and effectiveness of both the hormonal contraceptive and the antiretroviral drug. Thus, if a woman on antiretroviral treatment decides to initiate or continue hormonal contraceptive use, the consistent use of condoms is recommended. This is both for preventing HIV transmission and to compensate for any possible reduction in the effectiveness of the hormonal contraceptive. When a COC is chosen, a preparation containing a minimum of 30 mcg ethinylestradiol (EE) should be used.
b) Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	2	2	2	2	
c) Ritonavir-boosted protease inhibitors	3	3	3	3	
Anticonvulsant Therapy					
a) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	3	3	3	2	Clarification: Although the interaction of certain anticonvulsants with COCs, P or R is not harmful to women, it is likely to reduce the effectiveness of COCs, P, or R. Use of other contraceptives should be encouraged for women who are long-term users of any of these drugs. When a COC is chosen, a preparation containing a minimum of 30 mcg of EE should be used. Clarification: The recommendation for lamotrigine does not apply when lamotrigine is already being taken with other drugs that strongly inhibit (e.g., sodium valproate) or induce (e.g., carbamazepine) its metabolism, since, in these cases, the moderate effect of the combined contraceptive is unlikely to be apparent.
b) Lamotrigine	3	3	3	3	
Antimicrobial Therapy					
a) Broad-spectrum antibiotics	1	1	1	1	Clarification: Although the interaction of rifampicin or rifabutin therapy with COCs, P, R, or CICs is not harmful to women, it is likely to reduce the effectiveness of COCs, P, R, or CICs. Use of other contraceptives should be encouraged for women who are long-term users of either of these drugs. When a COC is chosen, a preparation containing a minimum of 30 mcg EE should be used.
b) Antifungal	1	1	1	1	
c) Antiparasitics	1	1	1	1	
d) Rifampicin or rifabutin therapy	3	3	3	2	

1. A condition for which there is no restriction for the use of the contraceptive method
2. A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3. A condition where the theoretical or proven risks usually outweigh the advantages of using the method
4. A condition which represents an unacceptable health risk if the contraceptive method is used.

Adapted from World Health Organization. *Medical Eligibility Criteria for Contraceptive Use.* 4th ed. Geneva, Switzerland: World Health Organization; 2009. http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf. Accessed December 2, 2013.

Interactions With Other Drugs

With the exception of rifampicin (Rifampin) or rifabutin, broad-spectrum antibiotics have not been shown to decrease the effectiveness of CHCs. Certain anticonvulsants and certain antiretrovirals can reduce effectiveness. During rifampicin or rifabutin use, it is suggested that additional contraceptive measures be used. For select anticonvulsants, a higher dose CHC can be used. For certain antiretrovirals, a DMPA or an IUD is a better choice. A current drug history should be taken when prescribing OCs, and the user should report new medications. For a brief list of various drugs and their interactions with COCs, refer to Table 1.6.

Starting and Stopping the Pill

The patient may start on Sunday (Sunday start), on the first day of menses (first day start), or immediately (quick start). The quick start is recommended by many experts because it mitigates confusion about instructions, pregnancy before pills are started, or forgetting to fill the prescription. For a Sunday start, the patient is instructed to begin taking her pills on the first Sunday after the onset of menstruation, which avoids withdrawal bleeding on the weekends. If menstruation begins on a Sunday, the first tablet is taken that day. For the quick start and Sunday start methods, a negative pregnancy test and backup contraception for the first 7 days are required. For patients beginning a first day start, they are instructed to take their first pill on the first day of menses. Patients are also instructed to take their pills at the same time each day and to use some type of mnemonic or cue to avoid missing pills. Also, a discussion of emergency contraception is recommended for the possibility of imperfect use.

Missed Pills

If one pill is missed, the patient should take it as soon as possible and resume the rest of the pack as usual. Any time the patient misses two or more tablets, she should also use another method of contraception until she has taken a tablet daily for 7 consecutive days. If BTB occurs following missed tablets, it will usually be transient. The likelihood of ovulation occurring if only one or two tablets are missed is low. Newer formulations, with a decrease in the pill-free interval, decrease the likelihood of ovulation if pills are missed during the early part of the cycle. Further instructions for patients can be found in Table 1.7.

Discontinuation of the Pill

Return to fertility is rapid following discontinuation of today's low-dose CHCs. A recent review showed that the pregnancy rates after 12 months of discontinuation was similar to that of nonusers.[50] Allowing 2 to 3 regular cycles before attempting pregnancy is the ideal.

TABLE 1.7 Instructions for Patients Who Missed an Oral Contraceptive Pill

Consecutive Pills Omitted	Time in Cycle	Instructions to Patient
1	Any time	Take missed pills immediately and next one at regular time
2	First week	Take two pills every day for next 2 days, and then resume taking pills on regular schedule.[a,b]
2	Third week	Take one pill every day until last day of third week.[a] Dispose of placebos and begin new pack next day.
≥3	Any time	Take one pill every day until last day of that week. Dispose of placebos and begin new pack next day.[a]

In the event of vomiting, the dose must be repeated or inserted vaginally.
[a]Additional contraceptive measures should be used as soon as the omission of oral contraceptive pills is discovered. These additional measures should be used for at least 7 days.
[b]EC should be taken in the event of unprotected intercourse if two or more pills are missed in the first week.

STEROIDAL CONTRACEPTION: OTHER

Progestin-Only Contraceptive Pill

The progestin-only pill is an alternative for breast-feeding women and women with conditions that preclude the use of estrogen, yet they still retain many of the advantages of CHCs: decreased blood loss, menstrual cramping, and premenstrual syndrome symptoms.

All progestin-only contraceptives cause bleeding pattern changes.[51,52] Approximately 40% of patients will ovulate with the progestin levels achieved with a progestin-only regimen. Although the exact mechanism(s) of action are unknown, it is known that the cervical mucus becomes thick and hostile, rendering it relatively impermeable to sperm. In addition, the endometrium is out of phase, making nidation less likely.

Progestin-only contraceptives can be used by almost every woman and have few medical contraindications (active liver disease or liver tumor being one). Early postpartum administration may slow involution of the uterus after delivery and prolong postpartum spotting and bleeding. A major disadvantage is that they must be taken at the same time every day. Therefore, emergency contraception should be taken if there is a delay of 3 hours or more.

Injectables

Depo Medroxyprogesterone Acetate

DMPA is the only injectable contraceptive available in the United States, although Cyclofem and Mesigyna (combination injectables) are available in other countries.

The typical side effects of DMPA concern menstrual changes, particularly with episodes of unpredictable irregular bleeding during the first months of use. A review of several studies determined that 37.5% of users experienced irregular bleeding and 27.7% prolonged bleeding in the first 3 to 6 months of use.[52] With increasing duration of use, these episodes decrease and amenorrhea becomes common. If BTB persists, the next dose of DMPA can be given early or conjugated estrogens (1.25 mg) or EE (2 mg) may be given daily for 7 to 14 days for several cycles. Approximately 50% of women who use DMPA for 1 year report amenorrhea, and this is an advantage for women troubled with increased or irregular periods. By 3 years, approximately 80% of users are amenorrheic. Women may also complain of breast tenderness, weight gain, and/or depression.

Women with a history of long-term use of DMPA have lower bone mineral densities than nonusers, although this has not yet been associated with an increase in fracture rate, and numerous studies have shown this bone loss to be minimal and reversible.[53–56] It is recommended that this method not be continued for more than 5 years and that calcium intake be optimized. Bone mineral density scanning is not necessary and is a waste of resources.

Another concern with the use of injectable contraceptives is occasional delayed return of fertility following discontinuation. This is not related to the duration of use. After discontinuing DMPA (Depo-Provera) to become pregnant, 50% of women conceive promptly.[57] In a small proportion of women, fertility is not reestablished until as long as 18 months after the last injection. However, the use of DMPA has no permanent impact on the ability to conceive.[58] Counseling is required before initiation of this method, which is obviously not ideally suited for simple spacing of pregnancy.

In a placebo-controlled trial, there was no relationship between DMPA and weight change or in the balance of food intake and energy expenditure.[59] In other trials, weight gain was similar to women using other methods. However, in obese adolescents and Navajo women, weight gain was increased.[60]

Women with sickle cell anemia, congenital heart disease, fibroids, or those older than age 35 years who smoke are excellent candidates for DMPA. There is no increase in stroke risk or MI or VTE with use of DMPA.[59] There is no link with cervical cancer, no increase in breast cancer risk, and a decrease in the incidence of anemia and pelvic inflammatory disease.[62] Depo-Provera is an excellent choice for epileptics because the high progestin levels raise the seizure threshold.[63]

DMPA is not teratogenic and is safe for use in lactating women. Although it is preferable to delay for 4 to 6 weeks, it may be given immediately postpartum, even in women who are breast-feeding if the risk of immediate pregnancy is high. There is no good evidence that it exacerbates depression.[61]

A new subcutaneous formulation (DMPA-SC, 104 mg/0.55 mL) has the advantages of being less painful and the potential for patient administration. The efficacy and side effects are the same. Both formulations are effective within 24 hours; however, they should be initiated within 5 days of the last menstrual period or at anytime with a backup method for 7 days to err on the side of caution. Repeat injections should be given every 12 weeks but can be given as early as 11 weeks or late as 13 weeks.

Vaginal Contraceptive Ring

This is a vaginal delivery system for administering combination estrogen-progestin, which is changed monthly. The NuvaRing system consists of a flexible, nonbiodegradable vaginal ring containing etonogestrel and EE. In two clinical trials evaluating the safety and efficacy of the vaginal ring, pregnancy rates were between 1 and 2 per 100 woman-years of use.[64] It should be kept refrigerated before dispensing, and clinicians should be aware that it has a shelf life of only 4 months. The vaginal ring (outside diameter is 54 mm) is inserted by the woman and worn continuously for 3 weeks, after which it is removed for 1 week to allow for a withdrawal bleed. After this 1 week, a new device is inserted. The device can be inserted on days 1 to 5 of the menstrual cycle. In clinical trials, about 18% of the women and 30% of the men reported feeling the ring occasionally during intercourse. If this is a problem, the ring can be removed for intercourse but must be replaced within 3 hours. If the ring remains outside the vagina for longer than 3 hours, its efficacy may be compromised. If it is removed or expelled from the vagina for longer than 3 hours, a backup method of contraception for 1 week is recommended.[65] If displacement of the ring occurs, the patient may rinse it off and reinsert it within 3 hours of expulsion. If the ring is left in the vagina for more than 3 weeks, ovulation may continue to be inhibited for up to 2 weeks after the recommended-use period; therefore, it can be used continuously.[66]

The ring releases minimal amounts of EE into the circulation yet maintains efficacy and cycle control comparable to the OC. Clinically, there is less BTB with the ring than with any other hormonal contraceptive method, and although there appears to be no diminished efficacy with increasing body weight, it has not been studied in women weighing more than 200 lb.[67]

For noncontraceptive users starting use of the ring, an additional nonhormonal method of contraception is recommended for the first week following the first insertion. When backup nonhormonal contraception is used, diaphragms should be avoided because the contraceptive ring can preclude proper placement of the barrier contraceptive.

If switching directly from OCs, the ring can be inserted any time after the last active tablet is taken. When

switching from another method of birth control, the ring can be inserted when the previous method is discontinued.

On removal of the ring, follicle-stimulating hormone levels begin to rise almost immediately, and return to ovulation can be expected in several weeks.[68]

The most frequently reported side effects with the ring were vaginitis (13.7%), headache (11.8%), and leukorrhea (5.9%). It is believed that the ring has the same thromboembolic risk as CHCs. Discontinuation rates because of device discomfort are low (2.5%).[67]

Oil-based, local antifungal vaginal therapy has been shown to increase blood levels of the ring's active ingredients but should not have any effect on contraceptive efficacy. Tampons and water-based spermicides such as nonoxynol-9 (N-9) do not alter serum levels of the active hormones. There is no risk of toxic shock syndrome from the ring because the ethyl-vinyl-acetate ring is nonabsorbent.

Combination Hormonal Contraceptive Patch (Transdermal System)

The combination contraceptive transdermal system (Ortho Evra) consists of a 20-cm^2 matrix-type patch containing norelgestromin (the primary active metabolite of norgestimate) and EE. Due to its continuous delivery system, the patch is not associated with any peaks or valleys of serum hormonal concentrations, has overall higher levels of estrogen, and therefore may be more thrombogenic.

The Evra system uses a 28-day (4-week) cycle in which a new patch is applied each week for 3 weeks. There is a 7-day period in which no patch is worn (corresponding to the 7-day pill-free interval with OCs). In three large clinical trials with more than 22,000 cycles of use, the pregnancy rate (Pearl index) was approximately 1 per 100 woman-years of use.[69]

The recommendations for starting are the same as the pill. The start day is also referred to as the patch change day. A woman may change this day during the fourth week by applying a new patch early on the desired day. If a woman is in the first week of her cycle and has forgotten to apply a new patch, she should apply one as soon as she remembers but also use a backup method of contraception for the next 7 days. She should also note that her patch change day for successive weeks has also been changed. If she is in week 2 or 3 of her cycle, has forgotten to change the patch, and less than 48 hours have elapsed between her patch change day and recognition of the error, she simply needs to place a new patch. A backup method of contraception is not necessary, and her original patch change day remains the same. If more than 48 hours has passed, she should replace the patch, use a backup method of contraception, and note that her patch change date has changed.

If a woman is interested in changing from CHCs to the patch, she should apply the patch on the first day of her menses. No backup method of contraception is needed. If she is past the first day of withdrawal bleeding, she may apply the patch and use a backup method of contraception for the next week.

If the patch detaches (occurrence rate, 1.1%), it should be replaced immediately. Therefore, patient should be given a prescription for a replacement patch. Hormonal release from the patch is not significantly affected by treadmill exercise or exposure to cold water, whirlpool, or sauna. Efficacy and side effect profiles are not affected by the anatomic site of application (abdomen, buttocks, torso, or upper outer arm), although it should not be placed on the breasts.[70] Placement of the patch in an area where the skin stays taut (i.e., is not prone to wrinkle with movement or positions) is highly recommended. Makeup, lotions, or body oils should not be applied to where the patch will be placed, and on placement, the patch should be pressed firmly for 10 seconds to ensure complete adherence by all edges.

Efficacy of the contraceptive patch is lower in women weighing more than 198 lb or 90 kg, although this may not be completely related to the delivery system because a similar decrease in efficacy has been noted in women weighing more than 198 lb or 90 kg who are using combination OCs.[7,69] Clinical studies with the patch have shown a minimal effect on body weight with patch use.[71] Contraindications, warnings, and precautions are similar to combination OCs.

In the first two cycles of use, the patch was associated with a significantly higher incidence of breast discomfort (which was primarily mild to moderate in nature) in comparison to the CHC. By the end of the second cycle, there was no significant difference in breast discomfort between the two modalities.[72] The patch should not be applied to any skin disruptions (e.g., eczema or seborrheic lesions). The risk of VTE is the same at that for 35 mcg EE pills.[73]

BARRIER METHODS OF CONTRACEPTION

Patients using barrier methods should be instructed regarding use of emergency contraception.

Diaphragm

The diaphragm can be an effective method of contraception. Diaphragm failure rates for the first year are estimated at 13 to 23%.[74] When used faithfully, the failure rate is probably closer to 6%. The diaphragm is fitted by the practitioner in the office, preferably using actual diaphragms rather than rings. They are not a good choice for very anteverted or retroverted uteri. Sizes range from 50 to 105 mm in diameter, with most women using a size between 65 and 80 mm.

To fit the diaphragm, place the middle finger against the vaginal wall and posterior cul de sac. Lift the hand anteriorly until the index finger is against the back of the symphysis pubis. Mark this point with the thumb to approximate the necessary diameter of the diaphragm. Insert the corresponding ring or diaphragm. Both the practitioner and patient are to assess the fit. If it is too tight, a smaller size is chosen. If it is expelled with increased intra-abdominal pressure, a larger size is needed.

The diaphragm should be placed no more than 6 hours before intercourse. It should always be used with spermicide (about 2 teaspoons). It should be left in the vagina for about 6 hours, but no more than 24 hours, after coitus. Additional spermicide should be placed intravaginally without removing the diaphragm for each additional episode of intercourse. Oil-based lubricants should not be used with the diaphragm. After it is removed, it should be washed with soap and water, rinsed, and dried. Powders should never be used on the diaphragm. Periodic checks for leaks should be done. The diaphragm should not be exposed to light or extreme temperatures during storage.

The incidence of urinary tract infections (UTIs) among diaphragm users is about twice that of women using CHCs. This may be due to pressure on the urethra with the diaphragm in place or increased colonization of the vagina with *Escherichia coli*.[75,76] Voiding after intercourse is helpful in avoiding UTI. A single postcoital dose of prophylactic antibiotics may also be used. There are some parous women with relaxation of the anterior vaginal wall in whom proper fitting is difficult, although the flat metal spring diaphragm may be tried in such instances. Well-motivated, properly fitted, and instructed women find the diaphragm a very acceptable method of contraception. The diaphragm reduces the incidence of STIs, as well as cervical neoplasia, presumably by reducing acquisition of HPV and other pathogens.[77] However, women at high risk of acquiring HIV or who have the virus should also use condoms. With a change in weight greater than 10 lb or after each pregnancy, the postpregnant woman may need to be refitted with a diaphragm of another size.

Cervical Cap

Currently, the cervical cap devices approved for use in the United States include the cavity rim cervical cap, the Prentif, FemCap, and the Lea's Shield. Prentif comes in four sizes based on internal diameter size: 22, 25, 28, and 31 mm. FemCap is available in three sizes based on internal diameter size: 22, 26, and 30 mm. The Lea's Shield comes in only one size and does not require fitting by a clinician. Although Prentif is a latex cervical cap, FemCap and Lea's Shield are both made of medical-grade silicone. The silicone caps are advantageous for women with latex allergies, and silicone is believed to resist odor formation.

A practitioner experienced in the use of this device must fit the Prentif and FemCap to the size of the cervix. The dome of the cervical cap covers the cervix and the rim fits snugly into the vaginal fornices. The brim adheres and conforms to the vaginal walls. Approximately 50% of women can be properly fitted. Women with a long cervix, short cervix, small cervix, or one that is too anterior may not be suitable candidates for the cap. Unlike the diaphragm, the cervical cap may be used in women with relaxation of the anterior vaginal wall.

Women should be advised to check placement of the device prior to and after intercourse to confirm correct positioning; the possibility of emergency contraception in the event of dislodgment during intercourse should also be discussed. A follow-up exam after prescribing is recommended, and the patient should wear the device into the office so the clinician can confirm proper placement. If a speculum is used to determine proper placement, it should be inserted only halfway into the vagina to avoid inadvertent dislodgment of the cervical cap.

Prior to use, the cervical cap should be filled one-third with spermicidal jelly or cream, applied to the inside of the cap, which is then positioned over the cervix by hand or with a special applicator. The cap should be inserted no less than 20 minutes and no more than 4 hours prior to intercourse. It is advised that women insert the cervical cap prior to sexual arousal because lengthening of the vagina on arousal may make insertion and proper placement more difficult. After insertion and after each act of coitus, the cervix should be checked to ensure it is covered. The FemCap and Prentif should not be removed any less than 6 hours after intercourse and all cervical caps may be left in place for up to 48 hours. Removal of the Prentif or FemCap is done by exerting pressure on the rim to break the seal and easily removing it. Squatting seems to be the best position for removal of these devices. Cleaning of the device is best done with a mild soap. Heat, synthetic detergents, organic solvents, or sharp objects should not be used for cleaning purposes. The device should be inspected regularly for signs of puncture, perforation, or wear.

With FemCap, the past obstetric history can predict the necessary size about 85% of the time with nulliparous women most often using the small size, with parous women with abdominal modes of delivery requiring the medium, and with parous women with a history of vaginal delivery requiring the large size. In clinical trials with the FemCap, it was noted that the risk of pregnancy was twice as high for parous women using the large device in comparison to nulliparous women using the small device or parous women using the medium-size device. For this reason, parous women requiring the larger size should be strongly counseled about an increased risk for pregnancy when relying on the FemCap as the sole means of contraception.[78–80]

When used with a spermicide, Prentif first-year failure rates with perfect use are approximately 9%, but

with typical use, failure rates are estimated at 20% for nulliparous women and 26 to 40% for parous women.[81] Like other vaginal barrier methods, the cap is associated with increased incidence of UTIs, bacterial vaginosis, and vaginal candidiasis when used with a spermicide.[82] Cervical caps do not decrease the risk of transmission of STDs. They have been associated with disruption of the cervicovaginal epithelium, although the actual clinical ramifications of this are unclear.

The cervical cap should not be used in women with active vaginal, cervical, or pelvic infections or vaginal or cervical lesions. Use of the cap during menstruation is discouraged because of the possibility of an increased risk of toxic shock syndrome and endometriosis; this possibility is theoretical, and no clinical evidence exists to disprove or support this to date.

Sponge

The Today sponge is a physical and a chemical barrier that fits closely over the cervix, absorbs semen, and releases spermicide. It is available without a prescription. Another similar sponge that can be ordered via the Internet is the Protectaid sponge, which contains three spermicides, including a lower dose of N-9 that may reduce mucosal irritation. Whereas the Today sponge can be inserted immediately before coitus or up to 24 hours in advance, the Protectaid sponge should be inserted no more than 12 hours in advance. Both sponges should be left in the vagina for 6 hours after intercourse. The Today sponge can be used continuously for 24 hours.

Failure rates for the sponge are similar to use of spermicide alone and are higher than diaphragm use.[83] As with the cervical cap, parous women experience failure rates approximately double those of nulliparous women.[83,84]

Male Condom

Male condoms are the third most popular contraceptive method employed by married couples in the United States, following sterilization and OCs. First-year failure rates with condom use are reported to be 8 to 15%, although use of the condom by highly motivated couples has a failure rate of 2 to 4%.[85,86] Contraceptive failure rates are lower in women older than the age of 30 years, those who seek to prevent pregnancy rather than delay it, and women of higher socioeconomic-economic status and level of education.

Most current condoms are made of latex. There are also "natural skin" male condoms which are made of lamb's intestine. Newer materials such as polyurethane are also used for condoms. Allergic reactions to latex or chemicals in the latex can occur, either immediately or as delayed reactions.

Clinicians should never assume pre-existing knowledge on proper condom use on the part of their patients. It is important to place the condom on the penis before any genital contact occurs. Uncircumcised men must pull the foreskin back prior to placement. Before unrolling and applying the condom, air should be squeezed out of the reservoir and the tip of the condom should extend beyond the end of the penis. The condom must be withdrawn prior to loss of the erection. Condoms may break during vaginal intercourse or withdrawal; slipping and tearing are more common with polyurethane condoms than with latex ones, but polyurethane condoms are suitable for latex-sensitive users, and because they are thinner may offer enhanced sensitivity.[86] The principal disadvantage of the use of the condom relates to an interruption of sexual foreplay, which can be minimized by incorporating its application during foreplay.

Although water-based lubricants can be used with any type of condom, petroleum-based lubricants should not be used with natural skin or latex condoms because they markedly decrease the strength of condoms, even with only brief exposure times. Polyurethane condoms may be used with any type of lubricant.

Male condom use has risen since the mid-1980s in the United States primarily as an HIV protection method. A meta-analysis of 25 studies found that male condoms offered a protective efficacy of 84 to 87% to HIV infection.[81,87] The latex condom is the only male condom shown to effectively prevent HIV transmission; condoms made from lamb intestines are permeable to virus particles, such as HIV and herpes.[80] Theoretically, polyurethane condoms may offer similar HIV protection as the latex condoms, but this has not been clinically confirmed yet. Users must realize that to reduce the risk of HIV transmission, latex male condoms must be used with each and every act of sex.

In addition to the decreased transmission of HIV, latex condoms also offer good protection against other viral and bacterial STDs such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas* infections.[88] Debate exists as to the extent of protection they may offer in preventing transmission of the herpes and HPVs if virus particles are located on the groin or vulvar areas.[89,90]

Female Condom

The FDA approved the female condom in 1994 (Fig. 1.3). There are several studies that evaluated its use and effectiveness. One study included female employees of two hospitals in Cape Town, South Africa. Twenty-three of 52 participants used all 10 of the devices issued to them, 21 stated that they or their partner(s) did not enjoy using the method, and an additional 9 had other problems with it. One problem that has been reported is that the device is noisy. Sexual responsivity, however, was the same or better in 52%, and overall acceptability was 52%. Compared with the male condom, 50% of the women and 44% of their partners considered the device as good, or better than, the male condom.[91] In the initial

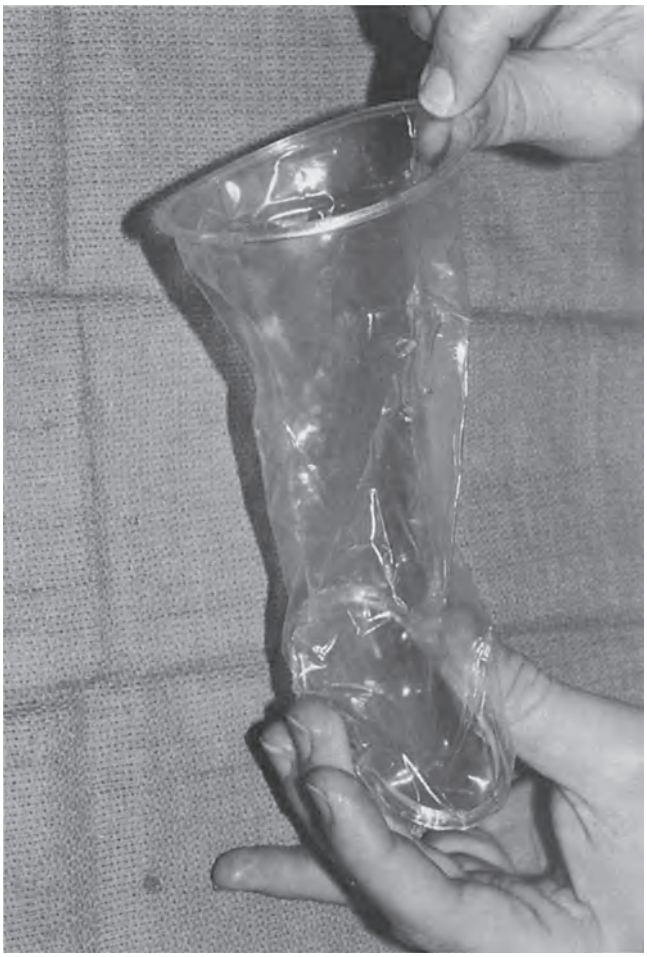

FIGURE 1.3 Female condom.

U.S. trial, there was a pregnancy rate of 15% in 6 months, although with perfect use the pregnancy rate is probably 3%.[92] The female condom should not be used with a male condom because this may increase slippage and/or breakage.[81]

Current experience shows that the female condom is an acceptable method for some couples. Although intended for single use only, some women reuse them for financial reasons. The female condom may be used for up to eight cycles of vaginal intercourse (and subsequent washing, drying, and relubrication with use) without any significant compromise to its structural integrity.[93] A clear advantage is that it is a female-controlled contraceptive that provides protection against STDs, including HIV. Directions regarding placement of the female condom can be found in Appendix 1.C.

SPERMICIDES

Spermicides are supplied as jellies, creams, foams, melting suppositories, foaming tablets, and soluble films. N-9 is the active ingredient in almost all spermicides available in the United States, and it works by disrupting the integrity of the sperm cell membrane.[81] Most spermicides employ N-9 in concentrations ranging from 3 to 20%. N-9 is not absorbed from the vagina. Other spermicides, such as octoxynol-9 or menfegol, are offered in some over-the-counter vaginal contraceptives, usually with 60 to 100 mg per vaginal application, but the FDA has stated that their efficacy and safety remain unproven.

Timing of the application of the spermicide is an important determinant of efficacy and although some must be inserted no more than 1 hour before coitus, others simply require enough time to melt or dissolve intravaginally prior to coitus. All must be reapplied for each act of intercourse. Aerosol foams offer better protection than the jellies, and melting suppositories provide poor intravaginal distribution.[94] The jelly, cream, and foam preparations are good for use up to 80 minutes prior to intercourse. The tablets and suppositories are good for 1 hour or less.

Efficacy of spermicides is highly product and user-dependent. Failure rates with perfect use are approximately 6%, whereas overall failure rates are approximately 26%. Unfortunately, the correct use of spermicides does not correlate with years of experience of use.[92]

Occasionally, spermicides may cause allergic reactions or yeast infections and may promote UTIs through alterations of the normal bacterial flora of the vagina.[81]

Since the mid-1980s, spermicides, including N-9, have been recommended for the prevention of STDs, including HIV. However, more recent studies indicate that N-9 causes an increase in genital ulcers and vaginal inflammation.[95,96] This raised concerns regarding the possibility of increasing the risk of HIV transmission. Several randomized trials have been performed more recently to evaluate the effectiveness of N-9 in prevention of STDs. Three different preparations of N-9 have been examined, including film, gel, and vaginal sponge. These investigators concluded that N-9 is not effective in preventing gonorrhea, chlamydia, trichomoniasis, syphilis, or HIV infection.[95,98,99] In addition, in one study using vaginal sponges with N-9, there was nearly a 50% increase in the transmission of HIV compared with the placebo group.[97] As a result of these findings, the Centers for Disease Control and Prevention (CDC) no longer recommends the use of spermicides containing N-9 for vaginal or anal intercourse.[99]

The use of spermicides does not increase the risk for spontaneous abortion, birth defects, or low birth weight.[100]

EMERGENCY CONTRACEPTION

Emergency contraception (EC), also known as postcoital contraception or the "morning after" pill, has been available for more than 30 years. These products delay ovulation and interfere with sperm transport but do not abort the zygote.

Three products—Preven, Plan B, and Ella—are currently approved by the FDA for the use of emergency contraceptive. Preven is simply the Yuzpe regimen (two doses of two COC tablets taken 12 hours apart, each with a combination of 50 mcg EE and 250 mcg LNG), which includes a pregnancy test and patient instructions. Plan B is a progestin-only formulation (LNG) that can be taken up to 72 hours after unprotected intercourse (but may be effective for up to 120 hours). Ella (30 mg ulipristal acetate, a selective progesterone receptor modulator) was recently approved and is effective up to 120 hours (5 days post risky intercourse).

A WHO-sponsored study demonstrated that the LNG regimen is more effective than the Yuzpe method. The proportion of pregnancies prevented in the LNG group was 85% (compared with the predicted rate that would have occurred with no EC), whereas the Yuzpe method prevented only 57% of pregnancies.[101] Ella had a similar efficacy to LNG in the first 72 hours.[102]

Treatment efficacy of EC is related in part to the timing of the first dose and the sexual exposure. The sooner after exposure the first dose of EC is administered, the greater the efficacy. For all regimens, the greatest protection against pregnancy is offered within the first 24 hours after unprotected sex. It is important that the patient understands if she continues to have unprotected sex, she may still become pregnant.

Side effects are also less with the LNG and ulipristal regimens. About 50% of users of the Yuzpe regimen experienced nausea and 20% report vomiting. In comparison, 23 and 6% had nausea and vomiting for the LNG regimen versus 15% and less than 5% for ulipristal.[102,103] As a proactive approach, it is recommended that an antiemetic be taken 1 hour prior to the first postcoital Yuzpe dose.[104] For all progesterone-only regimens, efficacy was less in women with a BMI greater than 30.

Both WHO and the International Planned Parenthood Federation find no absolute evidence-based contraindications to the use of EC, except for a known established pregnancy (e.g., a positive pregnancy test). The FDA-approved labeling in the United States does list clotting problems, ischemic heart disease, stroke, migraine, liver tumors, breast cancer, and breast biopsies as contraindications. Because the duration of therapy is short, the usual medical contraindications to long-term use of steroidal contraceptives are probably not applicable to EC.[105]

Other formulations marketed for use as combination hormonal methods have been studied for the use as emergency contraceptives. For additional information on other regimens that may be useful for EC, see Table 1.8.

Insertion of copper IUDs within 5 days of unprotected sex is another method of providing EC. An emergency IUD insertion reduces the risk of pregnancy by about 99%.

TABLE 1.8 Emergency Contraceptive Regimens (Other Than Ella or Plan B)

Conjugated estrogens (Premarin) 30 mg twice a day × 5 days *or* 10 mg four times a day × 5 days *or* 25 mg IV immediately and again 24 h later
Ethinyl estradiol (Estinyl) 2.5 mg twice a day × 5 days *or* 5 mg four times a day × 5 days
Oral contraceptive regimens[a]
Ovral two tablets immediately and again 12 h later
Levlen, Levora, Lo/Ovral, Nordette, Tri-Levlen, or Triphasil four tablets immediately and again 12 h later

[a]In the event of vomiting, the dose must be repeated.

NATURAL METHODS

Fertility Awareness–Based Methods

Fertility awareness–based (FAB) methods, also known as the rhythm method or periodic abstinence, encompass six techniques: the standard days method, the TwoDay method, the calendar rhythm method, the basal body temperature (BBT) method, the ovulation method, and symptothermal method. These methods are an option for the patient who does not want or cannot use other contraceptive methods. All are based on the fact that pregnancy is most likely to occur for only about 6 days of the menstrual cycle.[4] This is based on the ability of sperm to live in the female reproductive tract for 5 days and the ovum lack of viability for more than 24 hours. These methods also use physical changes, such as BBT and changes in cervical mucus (copious, watery, thin, stretchy), to determine the fertile window. These methods are contraindicated in women with irregular cycles, perimenopausal women, and women who recently gave birth, had an abortion, recently stopped another form of birth control, or are currently breast-feeding because these situations make it very difficult to predict ovulation.

The failure rate of FAB methods with typical use is usually estimated as 12 to 25% per year, with the TwoDay and standard days methods being most effective. There are several reasons for this. A principal reason is that sperm may survive for up to 5 days in the fallopian tube or in the pelvic peritoneal cavity.[107] Also, ovulation can occur before or after days 10 to 17 of the menstrual cycle. In addition, strict compliance with abstinence may be unreliable and misinterpretations of cervical mucus changes may occur. FAB methods can be supplemented with the use of over-the-counter ovulation predictor kits, especially ones that detect both estrone-3-glucoronide and luteinizing hormone (LH), to more accurately assess when abstinence is necessary.[106]

Standard Days Method

In women with menstrual cycles of at least 26 days and not more than 32 days, instructions not to have unprotected intercourse on days 8 to 19 of the cycle are given. This is the simplest method to teach and the one that has the fewest

number of days requiring abstinence or barrier contraception. CycleBeads have been shown to be very helpful.[108]

TwoDay Method

This method is a simple method based on the presence or absence of cervical mucus. Patients avoid unprotected intercourse all days with increased, thin, clear, stretchy cervical secretions. Unprotected intercourse may resume when there are no secretions for 2 consecutive days. It can be used in women with any cycle length.

Calendar Rhythm Method

The calendar technique requires the woman to record the length of her menstrual cycle for 6 months. She then subtracts 18 days from her shortest cycle and 11 days from her longest cycle to determine her fertile period and abstains from intercourse during that time. For example, if a woman's cycle averages 27 to 31 days, her fertile period would start on day 9 of her menstrual cycle (including the first day of her cycle in the count) (27 − 18 = 9) and end on day 20 of her menstrual cycle (including day one of her cycle in the count) (31 − 11 = 20). This method is not recommended for women whose cycle is less than or equal to 25 days or if it varies by more than 8 days between cycles. It is more successful if used in combination with other periodic abstinence methods.

Basal Body Temperature

The determination of temperature is a way of estimating the day of ovulation in each cycle. A special thermometer is available, making it easier to determine if there is a rise in BBT. With the rise in progesterone that follows ovulation, there is an increase in the BBT of 0.5 to 1°F. The woman must check her temperature on awakening, but *before* arising, and record the reading on a graph. Abstinence from intercourse starts on the first day of menses and continues until there is at least a 3-day duration, consecutively, of elevated BBT. This technique requires a fairly long period of abstinence. It is worth remembering that weekends, which often involve later hours and arising later, will tend to cause an elevation of the BBT that may approach 0.4 or 0.5°F, so that only persistence of the elevation in following days will be a certain determinant that ovulation has occurred. It is also useful to remember that the progesterone-induced temperature elevation begins only *after* ovulation, which is why its usefulness is mainly retrospective.

Ovulation Method

The time of ovulation can be identified by the amount and consistency of cervical mucus, and in this case, imminent ovulation can be anticipated before it occurs. Endogenous levels of estrogen and progesterone directly influence the quantity and quality of cervical mucus. Women are taught to recognize these changes. Abstinence is recommended during the menses, and then may occur every other day (as not to confuse semen with a change in secretions) until the first appearance of a larger amount of very thin, slippery mucus. After that, abstinence resumes until 4 days after the last day the almost liquid-like discharge was present. Unprotected sex must be avoided for 14 to 17 days out of each cycle. A different approach is to avoid intercourse until after ovulation has occurred (as noted by BBT or cervical mucus). Ovulation can also be determined in advance by urinary measurements of luteinizing hormone and estradiol, but this often requires the expense of three to four determinations per cycle.

Symptothermal Method

This method combines the use of BBT, changes in cervical secretions, and other physical changes, such as mittelschmerz and cervical texture. It can be used by women with any type of cycle. It is cumbersome, however, and unprotected intercourse must be avoided for 12 to 17 days.

Lactational Amenorrhea Method

The contraceptive effect of lactation has been long recognized. A 2003 Cochrane review reported that lactational amenorrhea was 98% effective when three conditions were present: there is amenorrhea, the baby is exclusively or almost exclusively breast-fed on demand, and that the method is not relied upon for more than 6 months. If any of these criteria are not met, another method must be used.[109] Pregnancy rates with supplementation are approximately 2.9 and 5.9% at 6 and 12 months, respectively.[110] It is obvious that if menstrual periods resume (at least 2 days of bleeding), the risk of conception is increased, but lactation still appears to provide some additional protection against pregnancy, perhaps by imperfect ovulation and/or endometrial response.

STERILIZATION

Female Sterilization

Sterilization is one of the most common methods of contraception in the United States. Most procedures are done in an outpatient surgical setting, although some are done in private offices. The mortality rate for sterilization is 1.5 per 100,000 procedures. This is lower than the mortality associated with childbirth (10 per 100,000).[111] The average failure rate in the first year is 0.5% for female sterilization and 0.1 to 0.15% for male sterilization, with the actual rate being operator, patient, and technique dependent.[112] Techniques that rely on more equipment have a higher failure rate secondary to technical problems.[113,114] Female patients younger than age 35 years have a higher failure rate, as do women who are not lactating at the time of the procedure.

With sterilization currently being readily available, careful consideration and counseling is in order. This is particularly true of women younger than age 30 years, and the procedure should generally be limited to the patient who is presumably in a long-term relationship.

These criteria are obviously not the case when a disease is present that could be worsened by the complication of subsequent pregnancy. The median age at sterilization is 30 years, and there is a higher incidence of regret in women sterilized before age 30 years and among those who divorce and remarry. In certain ethnic cultures, a woman incapable of bearing children may be considered "damaged" to some degree. The question needs to be asked, "What if something happened to your partner, or to one of your children—would this change your mind?" The decision should be regarded as irrevocable and unseemly optimism for the possibility of uncomplicated reversal should be faced with facts of insurance payments, the increase in risk of ectopic pregnancy, and the greatly diminished chance of success in the event of any type of cauterization procedure. An informed consent should state the risk of failure and the increased rate of ectopic pregnancy in that event.

Currently, the four most commonly used methods of sterilization in the United States include sterilization in conjunction with cesarean section or other abdominal surgery, immediate postpartum partial salpingectomy, minilaparotomy, or laparoscopy. An interval minilaparotomy approach would certainly be appropriate if the patient's history or pelvic findings suggested the possibility of significant pelvic adhesions and perhaps distortion of anatomy.

A more recently published, multicentered, prospective, cohort study involving 10,685 women was reported from the U.S. Collaborative Review of Sterilization (CREST). The CREST data show that failures continue beyond the first year: By 5 years, more than 1% of women had a sterilization failure, and by 10 years, 1.8% failed.[115] It is well known that the risk of ectopic pregnancy after tubal sterilization is greatly increased. Failures of sterilization are associated with a higher rate of ectopic pregnancies, with the incidence depending on the surgical procedure originally performed. Bipolar cauterization has a higher incidence of ectopic pregnancy associated with tubal failures than mechanical occlusion.[116] Another study found 7.3 tubal pregnancies per 1000 procedures, and found that bipolar tubal coagulation before the age of 30 years had a probability of ectopic pregnancy 27 times greater than women of similar age who underwent postpartum partial salpingectomy.[117] The same study also showed that a history of tubal sterilization does not rule out the possibility of ectopic pregnancy, even 10 years after the procedure.[117] The overall risk for ectopic pregnancy in sterilized women, however, is still lower than if they were not sterilized.

The first suggestion of a "post-tubal syndrome" was in 1951.[118] The CREST multicenter prospective study on this subject showed that of patients interviewed immediately prior and again poststerilization for up to 5 years, 35% report higher levels of menstrual pain, 49% reported very heavy increase in menstrual flow, and 10% reported increased spotting between periods, at the fifth year. During the first year, a lesser degree of pain and hypermenorrhea was found.[119] It is obvious that aging of the cohort may be a factor, as well as the fact that it takes such changes a significant time to develop. In similar, paired studies of poststerilization on women conducted several years apart, both Rulin and DeStefano showed an increased prevalence of pain in the latter studies.[120–123]

There have been anecdotal reports about the prevalence of hysterectomy after sterilization. Hillis et al. reported that the cumulative probability of undergoing hysterectomy within 14 years after sterilization was 17%.[124] The highest likelihood occurred among women who reported a history of endometriosis or noted prolonged bleeding prior to sterilization. Not surprisingly, women with gynecologic disorders were at greater risk of hysterectomy than were women without these disorders.[124] Women may be reassured that there is no detrimental effect on sexual response associated with tubal sterilization.[125]

A noncontraceptive benefit of tubal ligation is the reduction of ovarian cancer. Multiple small studies, flowed by a meta-analysis in 2011 have shown significant reductions for most types of ovarian cancer.[126] In fact, there has been evidence that bilateral salpingectomy alone reduced the cancer risk in *BRCA1/BRCA2* carriers.[127]

The FDA has approved two hysteroscopic methods of permanent female sterilization, the Essure in 2002 and Adiana in 2010. They can be performed in the office or outpatient. Both work after implants are placed in the fallopian tubes, inducing scar tissue formation and eventual occlusion. Women must use alternate forms of contraception at least for 3 months after the procedure and until proper implant placement is confirmed by hysterosalpingography. Because the Adiana procedure uses a silicone insert and radio-frequency ablation to occlude the tube instead of a nickel insert, evaluation of tubal occlusion can be more difficult. The Adiana insert is smaller and, theoretically, could cannulate tubes (with distal blockage or spasm) that the Essure could not. A notable difference is the resultant clinical pregnancy risk, with the Essure reporting no pregnancies in 643 women with confirmed occlusion for over 9 years. In contrast, the Adiana procedure has reported 12 pregnancies in 570 women over 5 years.[128] Bilateral placement rates were similar. However, bilateral occlusion was less with the Adiana system and more patients required a second procedure for bilateral occlusion with the Essure. Both procedures are tolerated well and have high satisfaction scores. At this point in time, the cost per patient is the same for the two procedures.[128]

Male Sterilization

Permanent surgical sterilization of men is done in the office and is safer, easier, and less expensive than surgical sterilization of women. In the "no scalpel" technique, a sharpened dissection forceps is used to pierce the skin and dissect the vas deferens. Complications are uncommon but may include some bleeding, hematoma formation, infection, or local reactions to anesthetics or sutures. A patent reanastomosis is achieved in approximately 86 to 97% of men seeking reversal of the vasectomy, although their fertility rates are considerably less due to a variety of issues.

CLINICAL NOTES

- In general, the estrogen-related contraindications are for those patients with cardiovascular disease, with thromboembolic disease or risks, and with liver disease. Hormone levels in pregnancy are far higher than those produced by contraceptive pills.
- Progestin-only methods and nonhormonal methods, such as the copper IUD, are a good option for women with relative or strong contraindications to estrogen.
- LARC methods (IUDs and implants) are safe and effective and should be considered first line, even in adolescent patients.
- Women should not be denied contraception because they do not have a recent Pap smear or STD screening.
- Healthy women older than age 35 years who do not smoke and are not obese can safely take CHCs.
- The need for safe and effective contraceptive methods remains great in the perimenopausal period as evidenced by the high unintended pregnancy rate in this age group.
- For perimenopausal women, CHCs or the vaginal ring should be the method of choice for nonsmoking, nonobese women to regulate menstrual periods, provide contraception, control vasomotor symptoms, protect bone health, and reduce the risk of endometrial and ovarian cancers.
- CHCs are contraindicated in the presence of cerebrovascular disease.
- CHCs are second-line in a patient with a history of classic migraine (migraine with focal neurologic symptoms or aura lasting more than 1 hour) due to an increased potential for stroke.
- There is no impact of CHCs on the pattern or frequency of seizures.
- Some anticonvulsants can decrease serum concentrations of estrogen and thus may increase the likelihood of intermenstrual bleeding among patients on CHCs but do not increase chance of pregnancy.
- Obesity is an independent risk factor for VTE and for contraceptive failure.
- For women with hypertension, if their blood pressure is controlled and no vascular disease is present, CHCs are not contraindicated.
- If a woman's triglycerides are above 350 mg/dL or in patients with familial hypertriglyceridemia, OCs should be avoided because they may precipitate pancreatitis and/or adversely affect the patient's risk for cardiovascular disease.
- In general, OCs can be safely used by women with MVP who are symptom free.
- Young diabetic women who are free of retinopathy, nephropathy, hypertension, or other complicating vascular disease(s) are appropriate candidates for low-dose contraceptives.
- Women with sickle cell anemia, congenital heart disease, or those older than age 35 years who smoke are excellent candidates for DMPA.
- Overall, the risk of breast cancer in women who take OCs until they are 55 years of age appears to be no different from that of nonusers.
- If prolonged immobilization is expected, stopping CHCs 1 month prior and use of a barrier method is advisable.
- The Mirena IUD releases 20 mcg LNG daily and has been approved for 5 years of use.
- The progesterone IUD may decrease blood flow by 40 to 50% and improve dysmenorrhea so its use may be preferable in women experiencing heavy or painful periods.
- The copper IUD has been approved for 10 years of use. It has the highest efficacy with the lowest cost.
- The copper IUD may increase menstrual flow up to 50% and can be mitigated by NSAID use. The increased menstrual flow subsides over time.
- If a pregnancy occurs with an IUD in place, the device should be removed as soon as possible, regardless of whether termination or pregnancy continuation is planned.
- Women who become pregnant with an IUD in place have an increased rate, approximately 50%, of spontaneous abortion. After removal of the IUD, the spontaneous abortion rate decreases to about 30%.
- Implanon, a single-rod subdermal implant the size of a matchstick, releases 68 mg of etonogestrel over 3 years. It does not affect bone mineral density.
- Few antimicrobial agents can interact with the pharmacokinetics and efficacy of sex steroid hormones present in OCs.
- In choosing a CHC, the optimal formulation will comprise the lowest effective dose with acceptable bleeding profiles and minimal side effects.
- Monophasic pills with 20 mcg EE are a good choice for new users.
- Yasmin and YAZ are both FDA approved for PMDD. These are also a good choice for polycystic ovarian syndrome, hirsuit, or hypertensive patients because drospirenone is antiandrogenic and a diuretic.
- The key to success in prescribing CHCs is an informed patient because unscheduled bleeding and side effects of are a major source of patient noncompliance and discontinuation.
- Extended cycle or continuous CHCs are an option for women with hormone withdrawal symptoms,

(continues)

dysmenorrhea, endometriosis, menorrhagia, or women who simply desire fewer menstrual cycles.
- Unscheduled bleeding is seen more frequently with continuous regimens but is reduced over time. Additional estrogen can be given to stabilize the endometrium.
- The quick start is recommended by many experts because it mitigates confusion about instructions, pregnancy before pills are started, or forgetting to fill the prescription.
- Although a third of women will experience irregular bleeding after the first 3 to 6 months of use, approximately 50% of women who use DMPA for 1 year and 80% for 3 years report amenorrhea.
- It is recommended that the DMPA method not be continued for more than 5 years and that calcium intake is optimized.
- A new subcutaneous formulation (DMPA-SC, 104 mg/0.55 mL) has the advantages of being less painful and the potential for patient administration.
- The NuvaRing system consists of a flexible, nonbiodegradable vaginal ring containing etonogestrel and EE that is worn for 3 weeks. The vaginal ring should be kept refrigerated before dispensing, and clinicians should be aware that it has a shelf life of only 4 months.
- There is less BTB with the vaginal contraceptive ring than with any other hormonal contraceptive method.
- The efficacy of the vaginal contraceptive ring has not been studied in women weighing more than 200 lb.
- The contraceptive patch system uses a 28-day (4-week) cycle in which a new patch is applied each week for 3 weeks. There is a 7-day period in which no patch is worn (corresponding to the 7-day pill-free interval with OCs).
- Hormonal release from the contraceptive patch is not significantly affected by treadmill exercise or exposure to cold water, whirlpool, or sauna nor is it affected by the anatomic site of application (abdomen, buttocks, torso, or upper outer arm), although it should not be placed on the breasts.
- Patients using barrier methods should be instructed regarding use of EC.
- Because there is evidence that N-9 may actually increase the risk of HIV transmission, the CDC no longer recommends the use of spermicides containing N-9 for vaginal or anal intercourse.
- EC delays ovulation and interferes with sperm transport. This can be achieved by insertion of a copper IUD, or by the Yuzpe, Preven, Plan B, or Ella regimens.
- The greatest protection against pregnancy is offered within the first 24 hours after unprotected sex.
- Fertility awareness–based (FAB) methods, also known as the rhythm method or periodic abstinence, encompass six techniques: the standard days method, the TwoDay method, the calendar rhythm method, the BBT method, the ovulation method, and symptothermal method.
- Lactational amenorrhea is 98% effective when three conditions were present: the method is not relied upon for more than 6 months, there is amenorrhea, and the baby is exclusively or almost exclusively breast-fed on demand.
- Progestin-only pills are preferred for lactating women seeking oral hormonal contraception.
- The average failure rate in the first year after transabdominal sterilization is 0.5% for women as opposed to 0.1 to 0.15% for vasectomy, with the actual rate being operator, patient, and technique dependent.
- Both the Adiana and Essure hysteroscopic sterilization procedures can be performed in the office and require additional contraception until the hysterosalpingogram (HSG) confirms bilateral occlusion 3 months postprocedure.
- The Essure hysteroscopic procedure has reported no pregnancies in 9 years of follow-up, making it the most effective of all sterilization methods.

Appendix 1.A
Placement of the Copper Intrauterine Device

1. Can be inserted whenever pregnancy has been reliably excluded, including immediately postpartum or after abortion.
2. Confirm uterine size and position on examination.
3. Clean cervix with antiseptic (optional).
4. Apply topical anesthesia or paracervical block to cervix; place tenaculum on anterior lip of cervix for traction (if uterus is extremely retroverted, placing tenaculum on posterior lip of cervix may be more helpful).
5. Sound the uterus; do not place IUD if uterus sounds to less than 6 cm or greater than 9 cm (excluding postpartum/postabortion).
6. Document IUD lot number in chart and open IUD package, keeping contents sterile.
7. Wear sterile gloves; load the IUD into the insertion tube with the arms of the "T" folded *downward* into tube; do not leave the IUD in the insertion tube with the arms folded for more than 5 minutes.
8. Insert solid tube into bottom of insertion tube until it touches the bottom of the IUD.
9. Adjust the flange of the insertion tube to depth of uterus and to the plane in which the arms will open.

Make sure the horizontal arms and long axis of the flange lie in the same horizontal plane.

10. Place insertion tube into cervix/uterus until it touches fundus of uterus. The flange should be at the cervix. Hold solid rod stationary and retract the insertion tube no greater than 0.5 inch to release the arms.
11. Hold insertion tube still and remove solid rod only. After the solid rod is out, remove the insertion tube. Cut threads 2.5 to 4 cm beyond and perpendicular to os. Measure and record the length of the strings.

Appendix 1.B
Placement of Levonorgestrel-Releasing Intrauterine Device

1. Can be inserted whenever pregnancy has been reliably excluded, including immediately postpartum or after abortion.
2. Confirm uterine size and position on examination.
3. Clean cervix and upper vagina with antiseptic (optional).
4. Apply topical anesthesia or paracervical block to cervix; place tenaculum on anterior lip of cervix for traction (if uterus is extremely retroverted, placing tenaculum on posterior lip of cervix may be more helpful).
5. Sound the uterus; do not place IUD if uterus sounds to less than 6 cm or greater than 9 cm (excluding postpartum or postabortion).
6. Document IUD lot number in chart and open IUD package, keeping contents sterile.
7. Release the threads, hold the slider in the furthest upward position and pull on the threads to pull the IUD into the inserter.
8. Adjust the flange to the sounded length of the uterus and secure the threads into the cleft.
9. Wear sterile gloves; with the number facing up, carefully insert into the cervix with countertraction on the tenaculum until the flange is 1.5 cm from the cervix.
10. Hold the inserter steady and open the arms of the IUD by pulling the slider back until it reaches the mark. Wait a few seconds.
11. Advance the inserter up to the flange so that the IUD is in the fundus.
12. Pull the slider all the way down and withdraw it. Cut threads 2.5 to 4 cm beyond and perpendicular to os. Measure and record the length of the strings.

Appendix 1.C
Placement of the Female Condom

1. After removing the condom from the package, check to ensure the lubrication is spread evenly inside the pouch from the bottom to the top. If more lubricant is necessary, add more from the additional lubricant that is supplied.
2. Check that the inner ring is at the bottom, closed end of the pouch.
3. Hold the condom with the open end hanging down toward the ground. Squeeze the inner ring with your thumb and middle finger. It should look like a long, narrow "O."
4. With the other hand, separate the labia so the vagina is accessible. The hand holding the condom pushes the inner ring and pouch up into the vagina until the entire inner ring is just behind the pubic bone. (This is the same placement one uses for a diaphragm.) The condom should be inserted straight into the vagina; in other words, it should not be twisted. About 1 inch of the open end should remain in place outside the vagina.
5. During sex, the outer ring may move from side to side, which is normal. However, if it begins to slide or slip or is noisy during sex, add more lubricant.
6. If the outer ring begins to be pushed into the vagina, the female condom should be replaced, with extra lubricant around the opening of the new pouch or on the penis.
7. To remove the condom, squeeze and twist the outer ring, keeping the sperm and semen inside the pouch. The condom is not designed to be flushed down a toilet—it must be placed in the trash. It should *not* be reused.
8. A new condom must be used with every act of sex.
9. The female condom should not be used at the same time as a male condom. If used simultaneously, neither product will stay in place.

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CHAPTER 2

Uterine Abnormalities

Lubna Chohan

INTRODUCTION

History

As time has progressed, women's health issues have become increasingly important. Much of this can be contributed to the increased life expectancy of women and their added contribution to the work force. Life expectancy was 50 years of age for females in 1900.[1] In the United States in 2006, this increased to 80.2 years of age for females.[2] Women with excessive menstrual bleeding suffer both economic and psychosocial costs including discomfort and diminished quality of life. Work and school status can suffer from stained clothes, lost time, and extra cost of menstrual products. A survey of 2805 American women showed those that had increased menstrual flow during the prior year were more likely to be unemployed than women with a normal flow. It is estimated that the cost of this work loss is $1692 annually per woman.[3]

Definitions

Most definitions of normal menstruation include a cycle length of 21 to 35 days, duration of 7 days or less, and blood loss of less than 80 mL. These values come from a Swedish study done in 1966. About 500 women (ranging from adolescence through their 50s) were studied. Blood loss was estimated after collecting menstrual pads and tampons and using the alkaline hematin method. Median blood loss was 30 mL per month with 10% of women losing greater than 90 mL per month. Greater blood loss was found in perimenopausal women.[3]

Abnormal uterine bleeding is somewhat subjective as practitioners base their assessment on a patient's history. Even if a woman's menstrual blood loss is greater than 80 mL, many of them consider this to be normal. These patients oftentimes seek treatment once their quality of life is affected, not because of bleeding symptoms. For those with a blood loss of less than 80 mL per month, 25% of women will be anemic (hemoglobin less than 12 g/dL). For those with a blood loss of greater than 80 mL per month, 67% are anemic.[3] Table 2.1 includes other standard definitions regarding abnormal uterine bleeding. To note, heavy menstrual bleeding is a newer term for menorrhagia.[4]

Endocrinology and Pathology

The menstrual cycle is endometrial breakdown and remodeling in a cyclical fashion. This tissue has well-defined episodes of proliferation, differentiation, and breakdown. Menstruation occurs in response to the withdrawal of ovarian steroids. This causes the uterine functional layer (upper two-thirds of endometrium) to shed and regenerate on a regular basis. The functional layer is then replenished after menstruation by exposure to estradiol then progesterone.[5]

After menstruation, the vascular compartment of the endometrium comprising the spiral arteries and arterioles needs to be reconstructed. New endothelial cells are formed and growth begins of capillaries and smooth muscle cells to form larger vessels. The remodeling of the endometrial vasculature is a multifactorial and complex process.[5]

Prostaglandins have a role in endometrial pathology and subsequently abnormal uterine bleeding. Arachidonic acid is broken down into prostaglandins by cyclooxygenase (COX) and lipoxygenase (LOX). At the end of the menstrual cycle with progesterone withdrawal and shedding of the endometrial functional layer, there is an increase in COX-2 expression that lasts through the proliferative phase. Data suggests that prostaglandins produced by COX enzymes in the endometrium directly control endometrial angiogenesis.[5]

Treatment with COX enzyme inhibitors have been shown to reduce menstrual blood loss and points toward disturbances of prostaglandin pathways in menorrhagia.[5] With ovulatory abnormal uterine bleeding in the absence of underlying pathology (i.e., leiomyomas), there is no difference in circulating steroid hormones or endometrial histology when compared to women with normal menses. It has been shown that disturbances of arachidonic acid metabolism and angiogenic processes and elevated levels of prostaglandin E_2 (PGE_2) in endometrium are found in women with menorrhagia. A dual mode of action has been shown for COX inhibitors used in the treatment of menorrhagia: inhibition of prostaglandin synthesis and inhibition of PGE_2 binding to its receptor.[5]

Women with heavy menses have endometrial endothelial cells that proliferate more. Also, their spiral arterioles have less vascular smooth muscle cells. This then

TABLE 2.1 Definitions

Oligomenorrhea: Intervals between bleeding episodes vary from 35 days to 6 months
Amenorrhea: No menses for at least 6 months
Primary amenorrhea: Absence of menstruation in a 16-year-old with developed secondary sexual characteristics or in a 14-year-old with absent secondary sexual characteristics
Secondary amenorrhea: Absence of menses for 6 months in females with previously irregular menstrual pattern
Menorrhagia: Prolonged (more than 7 days) or excessive (greater than 80 mL) uterine bleeding occurring at regular intervals; also called **heavy menstrual bleeding**
Metrorrhagia: Uterine bleeding occurring at irregular but frequent intervals, the amount being variable
Intermenstrual bleeding: Bleeding of variable amounts occurring between regular menstrual periods
Polymenorrhea: Uterine bleeding occurring at regular intervals of less than 21 days
Dysfunctional uterine bleeding (DUB): Excessive uterine bleeding with no demonstrable organic cause (genital or extragenital). It is most frequent due to abnormalities of endocrine origin, particularly anovulation.

Data from Nelson AL. LNG-IUS: First-line therapy for idiopathic heavy menstrual bleeding. *The Female Patient*. 2010;35:39–43; Deligeoroglou E, Athanasopoulos N, Tsimaris P, et al. Evaluation and management of adolescent amenorrhea. *Ann N Y Acad Sci*. 2010;1205:23–32; Katz VL, Lentz GM, Lobo RA, et al. Abnormal uterine bleeding. In: Katz VL, Lentz GM, Lobo RA, et al, eds. *Comprehensive Gynecology*. 5th ed. St Louis, MO: Mosby Elsevier; 2007:915.

prevents proper vasoconstriction of these vessels and subsequent increased menstrual blood loss.[5]

ETIOLOGY

Anovulation

In adolescents, abnormal uterine bleeding is commonly related to anovulation from an immature hypothalamic-pituitary axis. This results in months to years of unpredictable ovulation after menarche.[6] For these first few years, normal cyclic progesterone production lags behind the normal development of GnRH and estrogen. In the first year after menarche, 85% of cycles are anovulatory. Four years after menarche, only 56% of cycles are ovulatory.[6] If menarche occurs earlier, there is a faster normalization of ovulation when compared to girls with a delayed menarche.[6]

Another source of anovulatory menstrual bleeding is polycystic ovarian syndrome (PCOS). This is thought to occur in up to 10% of adolescents[6] and 6 to 8% of reproductive-aged women.[7] Clinical features of PCOS include polycystic ovaries, anovulation causing menstrual irregularities, and hyperandrogenism causing hair growth and acne. It is also related to insulin resistance, obesity, and infertility. Reproductive and metabolic abnormalities of PCOS include overproduction of ovarian androgens, increased pituitary luteinizing hormone (LH) secretion, incomplete maturation of ovarian follicle development, and insulin resistance with compensatory hyperinsulinemia.[7] During times of chronic anovulation, there is prolonged unopposed estrogen which can lead to excessive endometrial proliferation. When the endometrial thickness grows beyond its available blood supply, the superficial layers slough and breakthrough bleeding occurs.[7]

Other causes of anovulation secondary to disturbances in the hypothalamic-pituitary-ovarian axis include stress, excessive exercise, eating disorders, thyroid disease, and menopausal transition.[8]

Hematologic Disorder

Bleeding disorders can cause abnormal uterine bleeding and should be evaluated, especially in the adolescent. It is estimated that bleeding disorders have a 2% community prevalence rate.[9] In women with heavy menstrual bleeding, bleeding disorders are reported at 10 to 20%[9] and even higher in adolescents (7 to 48%).[6] Other bleeding symptoms that are predictive of these diseases include bleeding after tooth extraction, epistaxis, prolonged bleeding after wounds, postoperative bleeding, postpartum hemorrhage, and family history of bleeding disorders. Platelet abnormalities (platelet function defects and thrombocytopenia) and von Willebrand disease (VWD) should be considered. The most common inherited bleeding disorder is VWD with a 1% incidence, but only 125 per million have a clinically significant bleeding disorder.[9]

Uterine Pathology

Leiomyomas

Leiomyomas (or myomas or fibroids) occur in 20 to 50% of women, making them the most common solid pelvic tumors in women.[10,11] Some studies show a prevalence of up to 80% in African American women and 70% in Caucasian women by 50 years of age.[11] This is the most common diagnosis for hysterectomy in the United States.[10] Myomas originate from smooth muscle cells of the uterus and are benign. They range in size, number, and location, including intramural (within the myometrium), subserosal (externally extending to the serosa), submucosal (internally impinging on the uterine cavity), and pedunculated. They are estrogen dependent and decrease in size during menopause and other hypoestrogenic conditions. There is a higher concentration of estrogen receptors in myomas than in adjacent myometrium. Fibroids bind 20% more estradiol per milligram of protein than myometrium.[10]

About 30% of fibroids become symptomatic (abnormal uterine bleeding and pelvic pressure).[11] Heavy menstrual bleeding occurs secondary to an obstructive effect of myomas on uterine vasculature and subsequent congestion in proximal myometrium/endometrium causing excessive bleeding during cyclic endometrial sloughing. Histologically, endometritis is often seen in tissue

overlying submucosal fibroids, which may also contribute to abnormal uterine bleeding.[10]

The transition of myomas to malignant tumors is extremely rare. It is thought that leiomyosarcomas may be unrelated to benign fibroids. In a study of about 1300 women with symptomatic fibroids undergoing myomectomy or hysterectomy, uterine sarcoma (leiomyosarcoma, endometrial stromal sarcoma, and mixed mesodermal tumor) was seen in 0.2%.[10] A more realistic percentage is likely much lower than 0.2% if you consider all women with fibroids; only a small percentage are symptomatic and require myomectomy or hysterectomy. As stated previously, fibroids decrease in size during menopause. If a rapid growth of myomas occurs in a menopausal patient, the concern for malignancy should arise.

Endometrial Hyperplasia and Cancer

As age increases, so does the risk of endometrial carcinoma. At the time of diagnosis, the median age is 61 years, with 75 to 80% of women being postmenopausal.[12] The prevalence of carcinoma in women age 40 years or younger varies from 2.9 to 14.4%.[12] In regards to endometrial hyperplasia, there is a 2 to 7% prevalence in premenopausal women.[12] The progression rate to endometrial cancer is 1% for simple hyperplasia (mean duration 10 years), 2 to 4% for complex hyperplasia (mean duration 10 years), 23% for atypical hyperplasia (mean duration 4 years), and 29% for complex atypical hyperplasia (mean duration 4 years).[12] Ninety-five percent of women with endometrial cancer present with postmenopausal bleeding as their only complaint. Of all women who have postmenopausal bleeding, 3 to 10% have endometrial cancer.[13]

Recommendations for endometrial sampling range widely from all women older than 35 years of age with abnormal uterine bleeding or those who do not respond to initial management in the United States to women older than 45 years of age with cyclical heavy bleeding, greater than 90 kg, or have other risk factors for carcinoma in New Zealand.[12] In one of the largest series studying the appropriate age for endometrial sampling, findings included atypical hyperplasia and carcinoma being significantly higher in women 45 to 50 years than in younger age women. They also found importance in distinguishing anovulatory abnormal uterine bleeding because this is more likely to lead to hyperplasia versus ovulatory bleeding. Other risk factors for hyperplasia and cancer included nulliparity; obesity (greater than 90 kg); polycystic ovaries with anovulation; family history of endometrial or colon cancer; tamoxifen treatment; and a triad of obesity, diabetes, and hypertension.[12]

Endometrial Polyps

Endometrial polyps are being diagnosed more frequently secondary to the improved quality of transvaginal ultrasound, saline-infusion ultrasounds, and hysteroscopy.[14] It is thought that estrogen stimulation of the endometrium plays a role in the creation of these polyps. Women who are symptomatic can have abnormal bleeding: intermenstrual bleeding, heavy menstrual bleeding, spotting, discharge, or postmenopausal bleeding. Asymptomatic premenopausal patients may have polyps that resolve spontaneously. Also, polyps less than 1 cm may resolve.[14]

In a systematic review and meta-analysis including 17 studies and over 10,000 patients, the association of menopause, abnormal bleeding, polyp size, and malignancy risk in regards to endometrial polyps were studied.[14] Endometrial neoplasia was found in 5.4% of postmenopausal patients compared to 1.7% of premenopausal patients. In regards to abnormal uterine bleeding, neoplasia was seen in 4.2% of women with symptomatic bleeding versus 2.2% of asymptomatic women. This review concluded that there is an increased risk of endometrial neoplasia in women with endometrial polyps who have symptomatic bleeding or are postmenopausal. Overall, an association with polyp size was not noted.[14]

In a smaller retrospective multicenter study, the malignant potential of endometrial polyps was studied in approximately 2000 postmenopausal women.[15] The prevalence of endometrial carcinoma was 0.1% for asymptomatic menopausal patients. This was 10 times lower than for symptomatic (any bleeding or spotting in the prior 6 months) patients. For asymptomatic women, the only variable significantly associated with cancer or hyperplasia was polyp diameter (larger than 18 mm).[15] Both of these studies conclude that there is a higher rate of cancer in women with symptomatic endometrial polyps.

Endocrine Disorder

Major endocrine causes of abnormal uterine bleeding and amenorrhea include polycystic ovarian syndrome, thyroid disease, and hyperprolactinemia. When prolactin is elevated, hypothalamic GnRH secretion is suppressed. This in turn can affect circulating estrogen levels and menstrual cycles. Causes of hyperprolactinemia include stress, thyroid disease, medications, and pituitary tumors. If prolactin is mildly elevated, this may be due to stress and the level should be remeasured. With hypothyroidism, the stimulating effect of thyrotropin-releasing hormone (TRH) in the pituitary gland can cause elevated prolactin. Prolactin is inhibited by dopamine. With antipsychotic drugs, these block dopamine receptors and subsequently increase prolactin. Also, with pituitary tumors, these place pressure on the pituitary stalk, obstruct dopamine flow, and cause prolactinemia. These patients are often treated with dopamine receptor agonists (i.e., bromocriptine or cabergoline).[16]

TABLE 2.2 Etiology of Abnormal Genital Bleeding

Cancer

Infection

Benign

Pregnancy

Uterus
- Polyps
- Endometrial hyperplasia
- Adenomyosis
- Leiomyomas

Cervix
- Polyps
- Ectropion
- Endometriosis

Vulva
- Skin tags
- Sebaceous cyst
- Condylomata
- Angiokeratoma

Vagina
- Gartner's duct cyst
- Polyps
- Adenosis

Trauma

Abuse

Foreign body

Pelvic trauma/straddle injury

Drugs

Contraception

Hormone replacement therapy

Anticoagulant

Tamoxifen

Corticosteroids

Chemotherapy

Dilantin

Antipsychotics

Systemic disease

Coagulation disorder
- von Willebrand disease
- Thrombocytopenia or platelet dysfunction
- Acute leukemia
- Factor deficiencies
- Advanced liver disease

Thyroid disease

Hyperprolactinemia

Polycystic ovarian syndrome

Chronic liver disease

Cushing syndrome

Hormone secreting adrenal and ovarian tumors

Renal disease

Emotional and physical stress

Smoking

Excessive exercise

Vulvar disease
- Crohn disease
- Behçet syndrome
- Pemphigoid
- Pemphigus
- Erosive lichen planus
- Lymphoma

Data from Goodman A. Initial approach to the premenopausal woman with abnormal uterine bleeding. UpToDate Web site. http://www.uptodate.com/contents/initial-approach-to-the-premenopausal-woman-with-abnormal-uterine-bleeding. Accessed December 2, 2013; DeSilva NK. Differential diagnosis and approach to the adolescent with abnormal uterine bleeding. UpToDate Web site. http://www.uptodate.com/contents/differential-diagnosis-and-approach-to-the-adolescent-with-abnormal-uterine-bleeding. Accessed December 2, 2013; Goodman A. Overview of causes of genital tract bleeding in women. UpToDate Web site. http://www.uptodate.com/contents/overview-of-causes-of-genital-tract-bleeding-in-women. Accessed December 2, 2013.

TABLE 2.3 Etiology of Abnormal Genital Bleeding by Age Group

Neonates
- Estrogen withdrawal

Premenarchal
- Foreign body
- Trauma/abuse
- Infection
- Urethral prolapse
- Sarcoma botryoides
- Ovarian tumor
- Precocious puberty

Early postmenarche
- Anovulation (hypothalamic immaturity)
- Bleeding diathesis
- Stress
- Pregnancy
- Infection

Reproductive years
- Anovulation
- Pregnancy
- Cancer
- Polyps
- Leiomyomas
- Adenomyosis
- Infection
- Endocrine dysfunction (polycystic ovarian syndrome, thyroid, pituitary)
- Bleeding diathesis
- Medications

Perimenopausal
- Anovulation
- Polyps
- Leiomyomas
- Adenomyosis
- Cancer

Menopause
- Atrophy
- Cancer
- Hormone replacement therapy

Data from Wilkinson JP, Kadir RA. Management of abnormal uterine bleeding in adolescents. *J Pediatr Adolesc Gynecol.* 2010;23(6)(suppl):S22–S30; Goodman A. Initial approach to the premenopausal woman with abnormal uterine bleeding. UpToDate Web site. http://www.uptodate.com/contents/initial-approach-to-the-premenopausal-woman-with-abnormal-uterine-bleeding. Accessed December 2, 2013; DeSilva NK. Differential diagnosis and approach to the adolescent with abnormal uterine bleeding. UpToDate Web site. http://www.uptodate.com/contents/differential-diagnosis-and-approach-to-the-adolescent-with-abnormal-uterine-bleeding. Accessed December 2, 2013.

Other endocrine disorders were discussed previously (i.e., PCOS).

In regards to causes of abnormal genital tract bleeding and causes by age groups, a more comprehensive list is included in Tables 2.2 and 2.3.

EVALUATION

Laboratory

A pregnancy test should be performed on patients with abnormal uterine bleeding. Other labs include complete blood cell count, thyroid-stimulating hormone, prolactin, LH, follicle-stimulating hormone, and liver and renal function tests.

When concerned about bleeding disorders, check a complete blood cell count, prothrombin time, activated partial thromboplastin time, factor VIII, and von Willebrand Factor (VWF) ristocetin cofactor and antigen. It is advised to screen for VWD before initiating hormonal therapy because exogenous estrogen can elevate VWF into a normal range, thus giving a false-negative result.[6] This is why pregnant women normalize their factor VIII, von Willebrand antigen level, and ristocetin cofactor activity and usually do not bleed during the pregnancy. However, they can start bleeding within a few days postpartum as these levels decrease.[9]

If clinical hyperandrogenism is present, also check testosterone and dehydroepiandrosterone sulfate (DHEA-S). If DHEA-S is elevated, then adrenal gland function should be investigated with 17OH-progesterone. If DHEA-S is greater than 700 mg/dL, consider late-onset type congenital adrenal hyperplasia as a diagnosis.[16] A list of laboratory tests to consider in the workup of abnormal uterine bleeding is included in Table 2.4.

Endometrial Sampling

There is not a worldwide consensus on when to perform an endometrial sampling. Some countries advocate endometrial sampling after 45 years or with risk factors for endometrial hyperplasia/carcinoma.[12] In the United States, with the American College of Obstetricians and Gynecologists (ACOG) support, the recommendation is

TABLE 2.4 Laboratory Workup for Abnormal Uterine Bleeding

Urine pregnancy test (or beta-hCG)
Complete blood cell count
Thyroid-stimulating hormone (TSH)
Prolactin
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Liver functio n tests
Renal function tests
If concern for bleeding disorder:
Prothrombin time
Activated partial thromboplastin time
Factor VIII
VWF ristocetin cofactor and antigen
Studies of platelet aggregation and release
If clinical hyperandrogenism is present:
Testosterone
Dehydroepiandrosterone sulfate (DHEA-S)
17-OH progesterone

Data from Wilkinson JP, Kadir RA. Management of abnormal uterine bleeding in adolescents. *J Pediatr Adolesc Gynecol*. 2010;23(6)(suppl):S22–S30; Deligeoroglou E, Athanasopoulos N, Tsimaris P, et al. Evaluation and management of adolescent amenorrhea. *Ann N Y Acad Sci*. 2010;1205:23–32.

for endometrial sampling in women older than 35 years of age with abnormal uterine bleeding or those who do not respond to initial management.[12] In 2009, an ACOG Committee Opinion stated that postmenopausal patients with an endometrial echo of 4 mm or less (by transvaginal ultrasound) had a malignancy risk of 1 in 917 and did not require an endometrial biopsy. There are limitations of ultrasound and will be discussed in the following section.[17]

Radiology Studies

Ultrasonography and Sonohysterography

Transvaginal ultrasound has its limitations as it is a technical procedure and not all uteri will produce a reliable endometrial stripe. This can be affected by leiomyomas, prior surgery, obesity, adenomyosis, and axial orientation. For these patients, sonohystography could be used. This can help distinguish if no pathology is present, a thick endometrium, or abnormalities (i.e., polyp, submucosal fibroid).[17] Initial imaging of choice when evaluating leiomyomas is ultrasonography secondary to its availability and low cost. Limitations of transvaginal ultrasound include difficulty detecting small myomas and subserosal myomas. It is also difficult to map myomas in large uteri and when multiple fibroids are present.[18]

The timing of an ultrasound is also important. In women who are not menstruating (postmenopausal or premenopausal on birth control pills), ultrasonography can be done at any time because endometrial thickness does not vary. For menstruating women, the ideal time for imaging is after the bleeding cycle ends, when the endometrium is at its thinnest.[17]

With imaging studies readily available, we are seeing more cases of incidental findings. For asymptomatic (nonbleeding) postmenopausal patients with an incidental finding of a thickened endometrial echo, there is no validation for intervention.[17]

Magnetic Resonance Imaging

When evaluating fibroids, ultrasound has some limitations, as discussed previously. Magnetic resonance imaging (MRI) outperforms transvaginal ultrasonography in preoperative evaluation of location, number and size of myomas, and sensitivity for pedunculated submucosal and subserosal fibroids and large fibroids (>8.5 cm).[18] See Figures 2.1 and 2.2.

MRI is often the imaging study of choice for preoperative evaluation for laparoscopic (or robotic) myomectomies. With these surgeries, there is a lack of equivalent haptic perception compared to open surgery. For this reason, MRI is preferred for fibroid mapping.[19] This is also the imaging study chosen for uterine artery embolization, which will be discussed later in this chapter.

MANAGEMENT

Medical

There are a wide variety of medications that can be used to manage heavy menstrual bleeding. Medical treatment

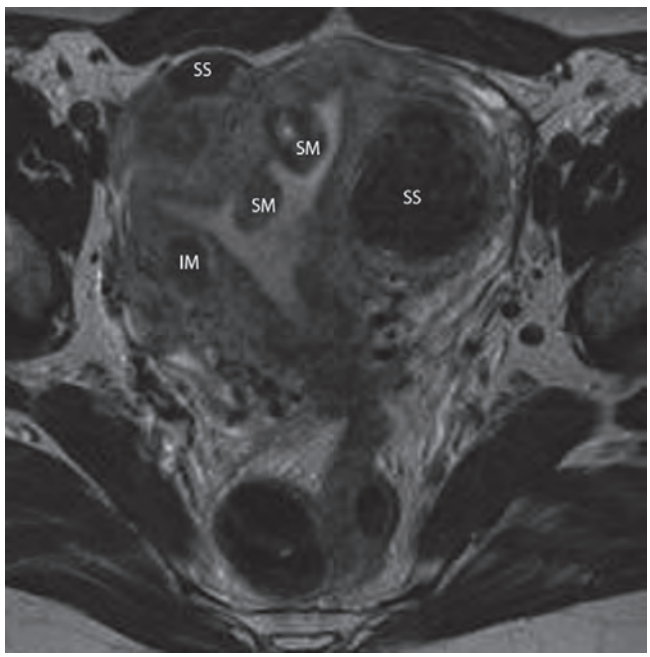

FIGURE 2.1 Coronal T2-weighted MRI shows multiple uterine submucosal (SM), subserosal (SS), and intramural (IM) fibroids. (From Griffin Y, Sudigali V, Jacques A. Radiology of benign disorders of menstruation. *Semin Ultrasound CT MR*. 2010;31[5]:414–432.)

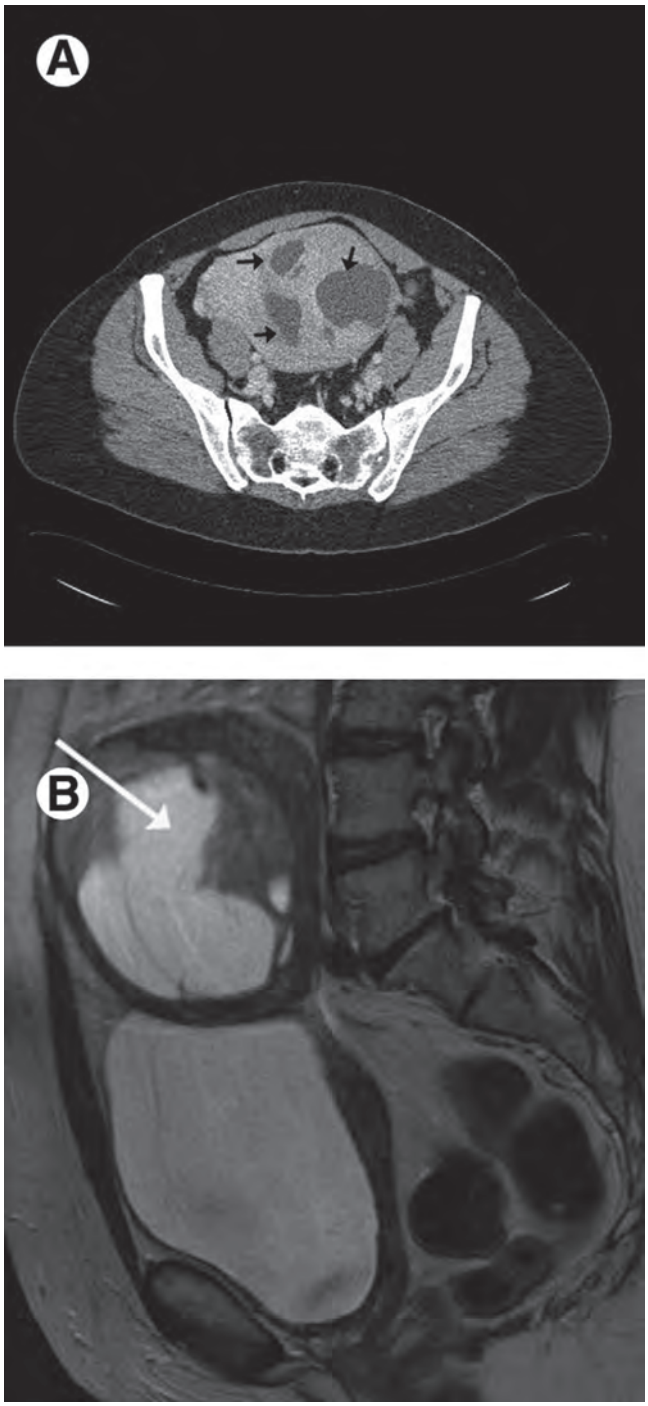

FIGURE 2.2 Cystic degeneration of fibroid. Axial CT image **(A)** and sagittal **(B)** T2-weighted MRI show cystic degenerating fibroids *(arrow)*. (From Griffin Y, Sudigali V, Jacques A. Radiology of benign disorders of menstruation. *Semin Ultrasound CT MR*. 2010;31[5]:414–432.)

avoids major surgery and the related morbidity but has to be taken long-term. The goal of this therapy is to improve quality of life, decrease blood loss, and reduce anemia. Menorrhagia is the most common cause of iron-deficiency anemia in Western women.[20] Table 2.5 contains medical and surgical treatment options.

TABLE 2.5 Treatment Options for Abnormal Uterine Bleeding

Medical Options	Surgical Options
Nonsteroidal anti-inflammatory drug • Salicylates (aspirin) • Indoleacetic acid (Indocin) • Aryl propionic acid derivative (naproxen, ibuprofen) • Fenamate (mefenamic acid) • Coxibs (celecoxib) Antifibrinolytic (tranexamic acid) Oral progesterone Intrauterine progesterone Combined estrogen/progesterone Other • Danazol • GnRH agonist (Lupron)	Hysterectomy Endometrial ablation • Thermal balloon • Circulated hot fluid • Cryotherapy • Radiofrequency electrosurgery • Microwave energy Myomectomy • Abdominal • Laparoscopic/robotic • Hysteroscopic Other • Uterine artery embolization • Magnetic resonance imaging–guided focused ultrasound surgery

GnRH, gonadotropin-releasing hormone.
Data from Oehler MK, Rees MC. Menorrhagia: an update. *Acta Obstet Gynecol Scand.* 2003;82(5):405–422.

Nonsteroidal Anti-Inflammatory Drugs

COX is the enzyme mostly responsible for conversion of arachidonic acid to prostaglandins. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX resulting in decreased levels of endometrial prostaglandins. NSAIDs are classified into five main categories (see Table 2.5). A meta-analysis of 16 randomized studies showed that one NSAID is not superior to another.[20] The fenamate NSAID group (mefenamic acid) has been studied extensively. This category has a unique property of inhibiting prostaglandin synthesis as well as binding to prostaglandin receptors, which are increased in women with menorrhagia.[20] Reduction in menstrual blood flow range from 22 to 46%.[20] Most studies of NSAIDs start the medication on the first day of menses and continue for 5 days or until menses ends.

The most common side effect of this medication is gastrointestinal symptoms. It should not be used in women with peptic ulcer disease.[20] Also, for women with bleeding disorders, NSAIDs should be avoided secondary to their negative effect on platelet aggregation.[6] Results of 17 randomized controlled trials show NSAIDs to be more effective than placebo, but not as effective as danazol, tranexamic acid, or levonorgestrel-releasing intrauterine system.[21]

Antifibrinolytics

Plasminogen activators are enzymes that facilitate the dissolution of clots and found to be at increased levels in women with heavy menstrual bleeding. These enzymes are inhibited by antifibrinolytics, which block conversion of plasminogen to plasmin and reduce fibrinolysis.[22]

Tranexamic acid is an antifibrinolytic that has been found to decrease menstrual blood loss by up to 50% and more effective than placebo, NSAIDs, and cyclic oral progestins.[20,22] Tranexamic acid has been used in Europe and Canada for years and is available over the counter in Sweden. In the United States, this medicine was previously approved only for use in dental extractions of hemophilic patients until November 2009 when the FDA approved use for heavy menstrual bleeding.[22]

Tranexamic acid is eliminated, largely intact, through urine with a half-life of 2 hours.[23] The recommended dose for women with normal renal function is 3900 mg daily (1300 mg three times a day) for as long as 5 days during menses.[22,23] There is a concern that tranexamic acid may increase the risk of venous thromboembolism (VTE) and is therefore contraindicated in women with a history of VTE.[22] It also has gastrointestinal side effects of nausea and diarrhea.[6]

Oral Progestins

Using progesterone-only therapy is based on the idea that women with heavy menstrual bleeding are anovulatory and progestins coordinate regular shedding when given in the late luteal phase (days 15 to 26). For women with ovulatory cycles, the use of progestins in the late luteal phase may not be beneficial.[20] Progesterone for 5 to 10 days has been shown to be ineffective for control of heavy menstrual bleeding when compared with tranexamic acid, NSAIDs, danazol, or intrauterine progesterone.[20] However, when norethisterone (15 mg per day) was used on days 5 to 26, there was a significant decrease in menstrual bleeding (87% compared with pretreatment levels).[20]

Intrauterine Progestin/Levonorgestrel-Releasing Intrauterine System

The levonorgestrel intrauterine system (LNG-IUS) delivers 20 mcg of levonorgestrel daily in a sustained-release formulation that lasts up to 5 years.[20] After 1 year of use, 20% of women report amenorrhea.[20] In a study of women with menstrual blood loss greater than 80 mL per cycle, including those with fibroids, the LNG-IUS was associated with a progressive decrease in blood loss over time. Results included a reduction of 78.7% at 6 months, 83.8% at 12 months, and 97.7% at 24 months.[21] There was also a significant increase in hemoglobin and ferritin levels and a superior outcome compared to oral norethindrone.[21] In a systematic review and meta-analysis of randomized controlled trials comparing LNG-IUS to endometrial ablation, 390 women were included (through six trials). Half of the studies used first-generation endometrial ablation (manual hysteroscopy) and the other half used second-generation ablations. There was no difference in reduction of menstrual blood loss between the different generation ablation devices.[24] Treatment failures were similar for ablation and LNG-IUS (18.9% for ablation and 13.4% for LNG-IUS).[24] Patients were followed for 2 years and LNG-IUS was found to have a similar efficacy to endometrial ablation in managing heavy menstrual bleeding and similar improvements in quality of life.[24]

When compared to hysterectomy, LNG-IUS is cheaper and associated with less morbidity. In a multicenter randomized study of 236 women with menorrhagia, patients either underwent hysterectomy or LNG-IUS placement. Thirty-one of 119 women with LNG-IUS had the device removed secondary to bleeding, spotting, or hormonal symptoms.[21] At 5 years, 58% of patients assigned to LNG-IUS chose to continue using this device instead of undergoing a hysterectomy.[21] Literature reviews consistently show that LNG-IUS is superior to NSAIDs, tranexamic acid, oral contraceptives, and danazol for treatment of idiopathic heavy menstrual bleeding.[4] In 2009, the Food and Drug Administration (FDA) approved LNG-IUS for treatment of heavy menstrual bleeding in women who use an IUD for contraception.[4] In 2008, the National Heart, Lung, and Blood Institute guidelines listed LNG-IUS as one of the top choices for treatment of heavy menstrual bleeding due to VWD.[4]

Progesterone Modulator

Antiprogesterone agents act at the level of the progesterone receptors, which are found in high concentrations in fibroid uteri.[25] An example is mifepristone (RU-486) which has been shown to inhibit ovulation and disrupt endometrial integrity.[20] Several studies show a 26 to 74% reduction in leiomyoma volume when high-dose mifepristone is used.[25] Fibroids have a slower rate of recurrent growth after cessation of mifepristone compared to GnRH agonists.[25] Up to 90% of women using mifepristone will have amenorrhea and note stable bone mineral density.[25] Side effects include endometrial hyperplasia without atypia and transient elevations in transaminase levels. Of 166 women who received 5 to 50 mg mifepristone for 3 to 6 months, 4% had a transient elevation in transaminases and 28% had endometrial hyperplasia.[26] Studies that used lower doses of mifepristone (2 to 5 mg) showed an absence of proliferative activity in the endometrium.[26] Further studies are needed for antiprogesterone agents being used in preoperative management of fibroids.[25]

Combined Hormonal (Estrogen-Progestin) Contraceptives

Several small studies and one randomized controlled trial show no difference between combined hormonal contraceptive (CHC), mefenamic acid, danazol, or naproxen.[21] Observational studies show a 50% decrease in menstrual blood loss with use of CHC.[21] Traditional oral contraceptives include 21 days of active pills followed by 7 days of placebo. Newer CHCs now contain more than 21 days of active pills. A Cochrane review in 2005 reviewed traditional CHCs in comparison to continuous or extended cycle CHCs through six

randomized controlled trials. Bleeding patterns were found to be equivalent or improved with continuous-dosing regimens in five of the six trials. However, increased spotting and breakthrough bleeding is seen with continuous-dosing CHCs.[21] One of these trials found that a pill with 1000 mcg of norethindrone acetate had less bleeding and spotting than pills with 100 mcg of levonorgestrel.[21]

Gonadotropin-Releasing Hormone Agonist

When gonadotropin-releasing hormone (GnRH) agonists are administered in a continuous fashion, a reversible hypogonadotropic state is created by downregulation of GnRH receptors. This will block ovarian function and cause a hypoestrogenic state.[20] Most patients develop amenorrhea and may have a 35 to 65% reduction in leiomyoma volume.[11,25] Leuprolide acetate is approved by the FDA for preoperative therapy in anemic women on iron with fibroids.[11,25]

The disadvantages of GnRH analogs include hypoestrogenic side effects of hot flushes and vaginal dryness. Recommendations include use limited to 6 months secondary to rapid bone demineralization, unless hormonal add-back therapy is used.[20] Once treatment is stopped, there is a regrowth of uteri and fibroids and bleeding issues return within several months.[25] GnRH analogs are highly effective for short-term use for fibroid shrinkage or endometrial thinning.[20]

Androgenic Steroid (Danazol)

Danazol is a derivative of 17 a-ethinyl-testosterone and acts on the hypothalamic pituitary ovarian axis to suppress ovulation and on the endometrium to produce atrophy.[20] It reduces menstrual blood loss by up to 80% and usually leads to amenorrhea at doses greater than 400 mg daily.[20] Danazol was found to be more effective than placebo, oral progesterone, NSAIDs, oral contraceptives, and LNG-IUS in nine randomized controlled trials.[21] Issues with danazol include its androgenic side effects experienced by 75% of patients: weight gain, oily skin, and deepening of the voice. If pregnancy occurs during danazol use, there is potential for virilization of the fetus.[20]

Desmopressin

Desmopressin (DDAVP) is a synthetic analogue of vasopressin, an antidiuretic hormone. It is used mostly for VWD (type 1) and hemophilia A for patients in prevention and treatment of bleeding episodes. DDAVP increases plasma concentrations of VWF and factor VIII and increases platelet adhesiveness. Using both DDAVP intranasal spray and oral tranexamic acid has been shown to be more effective in decreasing menstrual blood loss than DDAVP alone.[6] Also, by using both medications together, the dose and duration of DDAVP can be decreased. This reduces the potential risk of hyponatremia and water intoxication caused by the antidiuretic effect of DDAVP.[6]

Hemodynamically Unstable Patient

For patients who present with acute bleeding and are hemodynamically unstable, a history, physical exam, intravenous access and fluids, and possibly blood products should be given. In regards to medications to control the bleeding, intravenous estrogen can be used. Profuse uterine bleeding denudes the endometrium. Estrogen promotes rapid regrowth of endometrium over the denuded epithelial surface and increases coagulation factors (factor VIII, VWF) and platelet aggregation.[6,27] It is given at a dose of 25 to 40 mg IV every 4 hours for a maximum of 48 hours.[6] In a randomized controlled trial, patients were given IV Premarin (25 mg IV every 4 hours) or placebo for acute bleeding. The Premarin group was more effective in controlling blood loss and 64% stopped bleeding after the second dose (compared to 11% of the control group).[6] Antiemetics should also be used secondary to the nausea and vomiting associated with this treatment. CHC or progesterone should also be started and continued to maintain endometrial status because withdrawal of high-dose estrogen may induce further bleeding.[6,28] This can be given as medroxyprogesterone acetate 20 mg orally twice a day, norethindrone 5 mg orally twice a day, or a monophasic CHC.[28] Pulmonary embolism and thrombosis can be a potential complication of high-dose estrogen and should not be used in women with absolute contraindications.[27]

For those patients who do not respond to IV estrogen, consider surgical treatment with examination under anesthesia, dilation and curettage (for significant endometrial proliferation), and/or placement of a Foley catheter in the uterus to tamponade the bleeding until medications take effect. A catheter with a 30-mL balloon is used and inflated until resistance is met and bleeding stops. It should be removed within 24 hours of placement.[6]

Another alternative is tranexamic acid 1 g intravenous (or oral) and continued every 6 hours until bleeding stops.[6] For less severe bleeding, instead of IV estrogen, consider high-dose CHC. Three to four monophasic CHC are used daily for the first 5 to 7 days. Bleeding usually stops or decreases within 24 to 48 hours. Pills are then decreased to daily dosing.[28]

Surgical

Hysterectomy

More than 600,000 hysterectomies are performed annually in the United States, with 30 to 40% of these secondary to leiomyomas.[29] This is the second most common surgical procedure for reproductive age women in the United States after cesarean delivery.[29] Although hysterectomy cures menorrhagia and has a high patient

satisfaction rate, the perioperative morbidity ranges from 24% for vaginal hysterectomy to 43% for abdominal hysterectomy.[20] Complications include postoperative fever/infection, transfusion for hemorrhage, urinary and gastrointestinal lesions, anesthetic accidents, and cardiopulmonary events. Mortality rates are 6 to 11 per 10,000 women having hysterectomy for nonobstetric/nonmalignant conditions.[20]

Endometrial Ablation

For women with heavy menstrual bleeding, destruction of the endometrium by endometrial ablation has emerged as an alternative to hysterectomy.[30] First generation hysteroscopic methods include ablation and resection procedures (loop resection, laser, and rollerball cautery). Newer nonhysteroscopic (global) techniques include heated fluid, thermal balloon, radio frequency, microwave energy, and cryotherapy.

These global endometrial ablation devices are associated with shorter operative times and less complications (fluid overload, uterine perforation, cervical laceration, and hematometra). The success and complication rates compare favorably with traditional resectoscopic techniques.[31] Some contraindications to global ablation include pregnancy (or desire for future pregnancy), known or suspected endometrial hyperplasia or carcinoma, pelvic infection, uterine anomaly, and prior classical cesarean section or transmural myomectomy.[31]

The thermal balloon ablation (Thermachoice) consists of a balloon placed in the endometrial cavity and filled with 5% dextrose/water that is heated. Fluid pressure is adjusted to 160 to 180 mm Hg and temperature maintained at 87°C for an 8-minute cycle. Cryoablation (Her Option) uses a cryoprobe to create temperatures of −100°C to −120°C. The probe is placed within the endometrial cavity to form an ice ball. Circulated hot fluid ablation (Hydro ThermAblator) uses heated saline of 90°C for a 10-minute treatment cycle. During the active treatment phase, the fluid is heated under a low pressure of 55 mm Hg, which is less than fallopian tube opening pressures. Bipolar radiofrequency ablation (NovaSure) takes into account the uterine cavity length and width, which is entered into the radiofrequency controller. After passing a cavity perforation test, the device is deployed and tissue destruction begins with increasing tissue impedance. The procedure is terminated once impedance reaches 50 ohms or total treatment time is 2 minutes. Microwave endometrial ablation uses an applicator with resulting temperatures of 75 to 85°C. This heats to a depth of 5 to 6 mm with a treatment cycle time of 3 to 5 minutes in a normal size uterus.[31] Satisfaction and amenorrhea rates for these five global ablation techniques are included in Table 2.6.

In a 2008 retrospective study of over 3600 women undergoing endometrial ablation, risk factors and probability for hysterectomy were studied.[30] Results showed 21% had hysterectomy after ablation and 3.9% had a repeat uterine conserving procedure (repeat endometrial ablation, uterine artery embolization, or myomectomy). Indications for hysterectomy were vaginal bleeding, pain, or both. Pathology reports from the hysterectomies showed findings of myomas in 33%, adenomyosis in 24%, myomas and adenomyosis in 22%, and no pathology in 17%.[30] The most important risk factor for hysterectomy after ablation is age at time of ablation. Increasing age had less probability of hysterectomy. For women less than 40 years, the probability of hysterectomy is 40%. The presence of leiomyomas or type of endometrial ablation performed were not risk factors.[30]

Myomectomy

Myomectomy is a surgical option for women with symptomatic fibroids desiring uterine preservation. It was previously thought that abdominal myomectomy had a higher morbidity rate compared to hysterectomy, but more recent studies have disproved this.[25] A concern with myomectomy is the recurrence risk of

TABLE 2.6 Global Endometrial Ablation Devices

	Thermal Balloon (Thermachoice)[a]	Circulated Hot Fluid (Hydro ThermAblator)	Cryotherapy (Her Option)	Radiofrequency Electrosurgery (NovaSure)	Microwave Energy (MEA)
Year approved by FDA	1997	2001	2001	2001	2003
Cervical dilation	5	8	5	8	8.5
Cavity limits (cm)	4–10	10.5 or less	10 or less	6–10 (cavity length 4–6.5)	6–14
Approximate treatment time (min)	8	10	10–18	1.5	3.5
Satisfaction rate[b]	96%	—	86%	92%	99%
Amenorrhea rate[b]	13.9%	35.3%	22.2%	36.0%	55.3%

[a]Results listed above are for Thermachoice I. Newer studies show a satisfaction rate of 96% and amenorrhea rate of 37% for Thermachoice III.[32]
[b]Satisfaction and amenorrhea rates are at 12 months after procedure.
Data from Sharp HT. Assessment of new technology in the treatment of idiopathic menorrhagia and uterine leiomyomata. *Obstet Gynecol.* 2006;108(4):990–1003.

myomas. In a series of 125 patients followed for 5 to 23 years after myomectomy, recurrence risk was found to be related to number of myomas originally present. Of women with a single myoma, 27% had recurrence with 11% needing hysterectomy. Of women with multiple myomas, 59% had recurrence and 26% required additional surgery (repeat myomectomy, hysterectomy, or both).[25]

An alternative to the abdominal myomectomy is a laparoscopic approach. When minilaparotomy was compared to laparoscopy in almost 300 patients, the laparoscopic myomectomy was found to have a longer operative time but less blood loss, shorter hospital stay, less analgesic requirements, reduced length of postoperative ileus, and more rapid recuperation.[25] Blood loss is thought to be less during laparoscopy secondary to increased abdominal pressure from distension with carbon dioxide gas. This results in suppressed bleeding from small vessels. Also bleeding is magnified and more likely to be managed quicker.[19] In a case series of over 2000 patients with laparoscopic myomectomy who were followed for 6 years, the overall complication rate was 8 to 11% and subsequent pregnancy rate of 57 to 69%.[25] A concern with laparoscopic myomectomy is uterine integrity and subsequent rupture in pregnancy. With traditional laparoscopic instruments, it is more difficult to close the uterine defect in the same multilayered fashion as done during laparotomy. Now, with the increased dexterity of the robot, the same multilayered closure is more easily achieved.[11] Disadvantages of the robot include increased cost and decreased haptic sensation.[25]

For submucosal fibroids, the hysteroscopic approach can be used for myomectomy. Submucous myomas are classified by the amount of fibroid within the uterine cavity. Type 0 is a myoma that is completely intracavitary, type I is less than 50% of the fibroid is intramural, and type II is more than 50% of the fibroid is intramural. This system is predictive of whether complete surgical resection will occur, which is the best indicator for surgical success. In a study of almost 300 patients, the success rate was 95% at 1 year and 76% at 5 years.[25] The complication rate for hysteroscopic myomectomy is 1 to 5% in most studies (fluid overload with hyponatremia, pulmonary edema, cerebral edema, uterine perforation, gas embolism, infections, and bleeding intraoperative and postoperative).[25]

Other

Uterine Artery Embolization

The first report of fibroid embolization was published in 1995 with 16 patients treated in Paris. The procedure was done preoperatively to reduce bleeding. They found that in several patients, the fibroids had infarcted and decreased in size, making their hysterectomy unnecessary.[18] There are now 25,000 uterine artery embolization (UAE) performed worldwide annually.[29]

To perform UAE, the uterine arteries are catheterized (via femoral approach) and embolization particles are injected to cause fibroids to shrink. Particles preferentially flow into the larger tumor vessels, thus selectively devascularizing the fibroids and sparing normal myometrium. There are many different embolic agents; an example includes polyvinyl alcohol. The mean pelvic radiation dose is 6000 cGy/cm^2 in the United Kingdom, which is comparable to a barium enema. The mean estimated absorbed ovarian dose is 22 cGy with a mean fluoroscopy time of about 20 minutes.[18]

When compared to hysterectomy, UAE has a shorter hospital stay and faster recovery. Absolute contraindications to the procedure include pregnancy, concern for malignancy, and active infection. Results of UAE show a high success rate. Ninety percent of patients have improvement of menorrhagia or bulk-related symptoms. Within the first year of UAE, myomas and uteri decrease by up to 55% of their volume and continue to shrink over time. Women report an improved quality of life after the procedure.[18]

Patients with submucosal fibroids should be advised that these may spontaneously deliver and could occur months after UAE. Subserosal fibroids can also slough into the abdominal cavity and become infected or cause adhesions. Immediately after the procedure, patients may have pelvic pain which lasts for 24 hours. Postembolization syndrome may also start 1 to 5 days postprocedure. This is a pyrogenic reaction caused by breakdown products of the fibroids. Patients experience fever, nausea, and vomiting. It resolves in 7 days with NSAIDs/analgesics and should not be confused with infection.[18] Other complications include angiography-related complications, fibroid embolization complications, infections, chronic vaginal discharge, deep vein thrombosis, and ovarian failure. In women older than 45 years of age, ovarian failure is estimated at 15 to 43%.[18] A few theories are present, but the etiology is not clear. Embolic particles could migrate into the ovarian vessels through collaterals during the procedure; this may be likely in older women with an already decreased ovarian blood reserve. Ovarian blood flow may be diverted toward the uterus to maintain its viability after sudden occlusion from UAE. Another theory is that ovarian function is affected by occluding the uterine arteries.[18] See Figure 2.3 for pre- and post-uterine artery embolization MRI images.

In 2008, results from the FIBROID (fibroid registry for outcomes data) registry followed 3 years of outcomes after UAE in almost 1300 patients. Improved outcomes were seen in women with an initial complaint of heavy bleeding, smaller myoma size, and submucosal myomas. At 36 months after UAE, almost 30% of

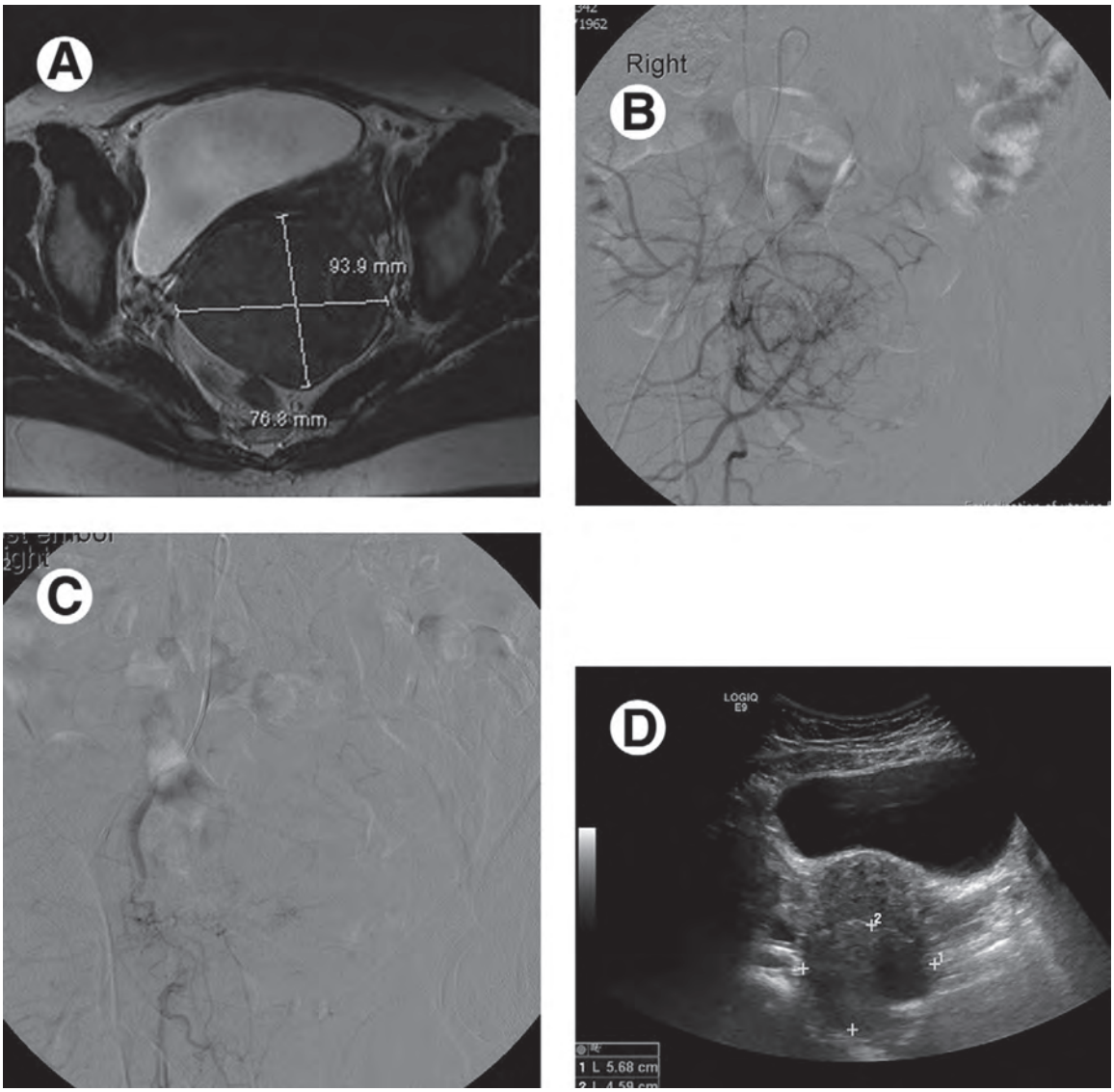

FIGURE 2.3 Embolization of uterine fibroid. Axial T2-weighted MRI **(A)** shows a large intramural fibroid. Angiographic images before **(B)** and after **(C)** embolization images showing reduced vascularity of the fibroid after the procedure. Follow-up ultrasonographic image **(D)** shows reduced size of the fibroid. (From Griffin Y, Sudigali V, Jacques A. Radiology of benign disorders of menstruation. *Semin Ultrasound CT MR*. 2010;31[5]:414–432.)

patients were amenorrheic (79% of these women were 45 years or older). During the 3 years following UAE, the percentage of patients who underwent a hysterectomy, myomectomy, or repeat UAE were 9.8, 2.8, and 1.8%, respectively. This is comparable to the reintervention rate after myomectomy of 5% per year.[29] Results of this study show a substantial improvement in symptoms and quality of life for the large majority of patients. Over 85% of these patients would recommend UAE to family members and friends.[29]

Magnetic Resonance Imaging–Guided Focused Ultrasound Surgery

Magnetic resonance imaging–guided focused ultrasound surgery (MRgFUS) was approved by the FDA in 2004. This modality uses high-intensity ultrasound waves directed into a focal volume of a myoma.[11] The ultrasound energy penetrates soft tissue and produces well-defined regions of protein denaturation, irreversible cell damage, and coagulative necrosis.[25] Outcomes of 109 patients who underwent MRgFUS were reported at 6 and 12 months. Uterine volume reductions were modest: 13.5% at 6 months and 9.4% at 12 months. Symptom reduction occurred in 71% of patients at 6 months and 51% of patients at 12 months.[25] Adverse events were low but included heavy menses requiring transfusion, persistent pain and bleeding, hospitalization for nausea, and leg/buttock pain from sonification of the sciatic nerve in the field which resolved. More long-term data is needed on this procedure.[11,25]

CLINICAL NOTES

- Normal menstruation includes a cycle length of 21 to 35 days, duration of 7 days or less, and blood loss of less than 80 mL.
- Withdrawal of ovarian steroids causes menstruation to occur where the upper two-thirds of the endometrium is shed.
- Arachidonic acid is broken down into prostaglandins by COX enzymes. Increased PGE_2 and disturbances in arachidonic acid metabolism are found in women with menorrhagia. COX enzyme inhibitors reduce menstrual blood loss.
- Anovulation is one cause of abnormal uterine bleeding. This can be due to an immature hypothalamic-pituitary axis, polycystic ovarian syndrome, stress, excessive exercise, eating disorder, thyroid disease, and menopausal transition.
- In adolescents with heavy menstrual bleeding, bleeding disorders are reported at 7 to 48%, with VWD being the most common inherited disorder.
- Leiomyomas are the most common solid pelvic tumors in women and the most common reason for hysterectomy in the United States. They are estrogen-dependent and decrease in size during menopause and other hypoestrogenic states. The transition to malignancy is extremely rare.
- Seventy-five to 80% of women with endometrial cancer are postmenopausal. Ninety-five percent of women with endometrial cancer present with postmenopausal bleeding as their only complaint. Of all women with postmenopausal bleeding, 3 to 10% have endometrial cancer.
- Endometrial polyps have a greater risk of malignancy in postmenopausal patients and those with symptomatic bleeding.
- Endocrine disorders that cause abnormal uterine bleeding include polycystic ovarian syndrome, thyroid disease, and hyperprolactinemia.
- Basic laboratory workup for abnormal uterine bleeding should include a pregnancy test, CBC, TSH, prolactin, FSH, LH, liver and renal function tests.
- Evaluation for abnormal uterine bleeding may include endometrial sampling, ultrasonography, sonohysterography, or MRI.
- NSAIDs inhibit COX resulting in decreased levels of endometrial prostaglandins and reducing menstrual blood loss.
- Tranexamic acid is an antifibrinolytic that decreases menstrual blood loss by up to 50%.
- Progesterone treatment for abnormal uterine bleeding is based on the idea that these women are anovulatory and progestins coordinate regular shedding.
- LNG-IUS was found to have a similar efficacy as endometrial ablation for management of heavy menstrual bleeding. Many women who would have otherwise chosen a hysterectomy were satisfied and continued with LNG-IUS use.
- CHC can decrease menstrual blood loss by 50%.
- GnRH agonists may reduce leiomyoma volume by 35 to 65% and induce amenorrhea. This is highly effective for short-term use.
- Danazol reduces menstrual blood loss by up to 80% but issues include androgenic side effects.
- DDAVP, alone or with tranexamic acid, is used for bleeding episodes in women with VWD and hemophilia A.
- For the hemodynamically unstable patient with acute bleeding, management may include IV estrogen, dilation and curettage, uterine tamponade, or tranexamic acid.
- Second-generation endometrial ablation (global techniques) include thermal balloon ablation, cryoprobe, circulated hot fluid, bipolar radiofrequency, and microwave energy. The most important risk factor for hysterectomy after ablation is age at time of ablation.
- Myomectomy is a surgical option for women with symptomatic fibroids desiring uterine preservation. This can be done abdominally, laparoscopically, or hysteroscopically.
- UAE causes a decrease in myomas and uteri by up to 55% of their volume within 1 year and continues to shrink with time. Patients may experience pelvic pain, postembolization syndrome, or ovarian failure.
- MRgFUS uses high-intensity ultrasound waves to decrease myoma volume. Most current studies have a 12-month follow-up of patients. More long-term data is needed on this procedure.

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CHAPTER 3

Hyperandrogenism

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Hyperandrogenism is the excess production and/or action of the male hormones testosterone and dihydrotestosterone, and their precursors—androstenedione and dehydroepiandrosterone. Hyperandrogenism affects approximately 5% of reproductive age women. The most common causes of hyperandrogenism include polycystic ovary syndrome (PCOS), idiopathic hirsutism, nonclassical adrenal hyperplasia (NCAH) due to a 21-hydroxylase deficiency and ovarian or adrenal androgen-secreting tumors. For women affected by hyperandrogenism, their chief complaints may include oligomenorrhea or amenorrhea, hirsutism, anovulatory infertility, and obesity. Hyperandrogenic women are at increased risk for type 2 diabetes, gestational diabetes, and the metabolic syndrome, including dyslipidemia and hypertension. Hyperandrogenism often begins insidiously early in puberty, and slowly and stealthily becomes progressively more severe until the full phenotype, including hirsutism and oligomenorrhea, emerges firmly established in late adolescence.[1] Hyperandrogenism is associated with both reproductive and metabolic abnormalities, including increased pituitary secretion of luteinizing hormone (LH) and insulin resistance in muscle and adipose tissue. Fortunately, most cases of hyperandrogenism are successfully treated either by using estrogen-progestin contraceptives to suppress the excess LH secretion and ovarian androgen overproduction or by using an insulin sensitizer to reduce the hyperinsulinemia that contributes to ovarian androgen overproduction.

ENDOCRINE BIOLOGY OF HYPERANDROGENISM

Androgens are those steroids that stimulate growth of the male secondary sex glands, such as the prostate. Androgens bind to the intracellular androgen receptor and alter the transcription of specific genes involved in the development of the male secondary sex phenotype. Testosterone (T) and dihydrotestosterone (DHT) are the biologically active androgens. Androstenedione (A) and dehydroepiandrosterone sulfate (DHEA-S) are important androgen precursors but have little inherent androgen activity. Hyperandrogenism is the state of increased androgen production and action. In most cases of hyperandrogenism, the ovary, the adrenal, and the pilosebaceous unit contribute to the androgen overproduction and action.

Two-Gonadotropin, Two-Cell Theory: Dual Defects Causing Hyperandrogenism

The ovarian follicle contains two main cell types: theca cells line the outer surface of the follicle and granulosa cells are within the inner core of the follicle. Theca cells express LH receptors and convert pregnenolone to androstenedione (Fig. 3.1). Granulosa cells from small follicles express follicle-stimulating hormone (FSH) receptors and convert androstenedione to estradiol, the main biologically active estrogen. In many cases of hyperandrogenism, there is an imbalance in the biological effects of LH and FSH, with too much LH effect and too little FSH effect. This results in excess secretion of androgen and insufficient conversion of estrogen to androgen, resulting in an androgen-dominant ovarian environment. When the gonadotropins LH and FSH are out of balance, the responding theca and granulosa cells are not collaboratively functioning and anovulation is the result.

All estrogen is derived from the androgen precursor, androstenedione. In the ovarian follicle from normally cycling women, there is a proper balance of LH and FSH activity resulting in the conversion of most androstenedione to estradiol and creating a follicular milieu that is dominated by estrogen and is healthy. In most cases of hyperandrogenism, the excess LH activity and the insufficient FSH results in excess accumulation of androstenedione and testosterone and insufficient production of estradiol, resulting in a follicular milieu that is dominated by androgen and is unhealthy. In these unhealthy follicles, the granulosa cells cannot grow to help the follicle to develop into a large preovulatory follicle, 18 to 25 mm in diameter. The growth of the follicle is stunted and remains in the size range of 2 to 9 mm in diameter. Little estrogen is secreted from these follicles resulting in no preovulatory surge of estradiol, which is the key factor that triggers the LH surge and ovulation. A hyperandrogenic ovarian environment is associated with disordered follicle growth, oligo- or anovulation, oligomenorrhea or amenorrhea, and increased circulating androgens.[2]

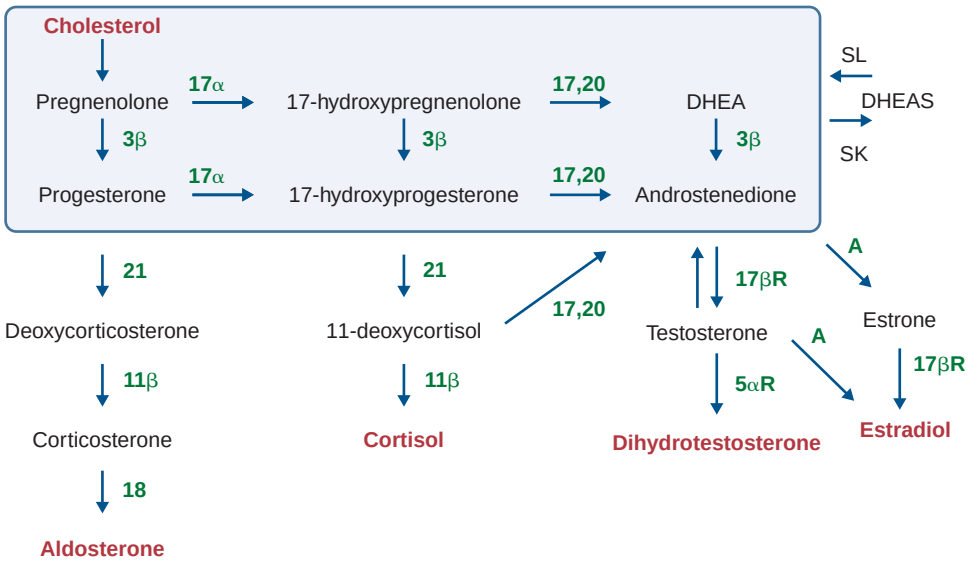

FIGURE 3.1 Steroidogenesis in the ovary and adrenal gland. Ovarian steroid synthesis is limited to the boxed reactions and conversion of androstenedione to estrone, estradiol, and testosterone. Adrenal steroid synthesis includes the production of aldosterone, a mineralocorticoid, and cortisol, a glucocorticoid. Adrenal synthesis of cortisol and androstenedione are delicately balanced. Notice that 17-hydroxyprogesterone can either be metabolized to a glucocorticoid, cortisol, or an androgen, androstenedione, depending on the kinetics of each pathway. A block of the enzyme 21-hydroxylase will force 17-hydroxyprogesterone into the androstenedione pathway. The first step in adrenal steroid synthesis is the combination of acetyl CoA and squalene to form cholesterol, which is then converted into pregnenolone. The enclosed area contains the core steroidogenic pathway used by the adrenal glands and gonads. 17α, 17α-hydroxylase (CYP17, P450c17); 17,20, 17,20 lyase (also mediated by CYP17); 3β, 3β-hydroxysteroid dehydrogenase; 21, 21-hydroxylase (CYP21A2, P450c21); 11β, 11β-hydroxylase (CYP11B1, P450c11); 18 refers to the two-step process of aldosterone synthase (CYP11B2, P450c11as) resulting in the addition of a hydroxyl group that is then oxidized to an aldehyde group at the 18-carbon position; 17βR, 17β-reductase; 5αR, 5α-reductase; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; A, aromatase (CYP19). (From Nieman LK. Adrenal steroid biosynthesis. http://www.uptodate.com/contents/adrenal-steroid-biosynthesis. Accessed November 18, 2013.)

Adrenal Cortisol and Androgen Secretion: A Delicate Balance

The main role of the adrenal gland is to secrete cortisol and aldosterone. However, given the organization of cortisol synthesis (Fig. 3.1), androgens are always produced as a "spill over" product from the cortisol pathway. The normal adrenal gland is delicately balanced to produce adequate amounts of cortisol without secreting excessive androgens. Unfortunately, minor reductions in any of the enzymes in the cortisol pathway can lead to excessive production of androgen. For example, in women with NCAH due to 21-hydroxylase activity, a decreased efficiency of the enzyme 21-hydroxylase due to a genetic defect causes a build up of a cortisol precursor, 17-hydroxyprogesterone (Fig. 3.1). Instead of 17-hydroxyprogesterone efficiently proceeding to cortisol, it is converted to androstenedione, which is then converted to testosterone and dihydrotestosterone. The partial block to cortisol synthesis results in an imbalance of the cortisol to androgen production ratio in the adrenal. The 21-hydroxylase defect is the cause of hyperandrogenism in about 5% of women with hyperandrogenism.

If adrenocorticotropic hormone (ACTH) stimulation of the adrenal is excessive, this causes an increase in both cortisol and androgen production, but the ratio of the two remains relatively normal. In Cushing disease, excessive ACTH secretion causes both excessive production of cortisol and androstenedione. Cushing disease is a rare cause of hyperandrogenism.

Dihydrotestosterone Is the Dominant Androgen in Target Tissues

In the hair follicle and other peripheral organs, androstenedione and testosterone are converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase. DHT binds to the androgen receptor with an affinity 10-fold higher than that of testosterone. The importance of DHT as the dominant androgen within cells is highlighted in individuals with inherited deficiencies of 5α-reductase. Males lacking this enzyme are phenotypically female at birth because they are unable to convert testosterone to DHT and are thus unable to activate a program of male differentiation during development. All hyperandrogenic women have excessive conversion of testosterone to DHT in peripheral tissues. This occurs because elevated DHT concentration in peripheral tissues, such as hair follicles, stimulates the synthesis of more 5α-reductase resulting in more rapid and efficient conversion of testosterone to DHT, a positive feedback loop. DHT is an intracellular steroid, and very little reenters the circulation, so it is not a useful target for blood measurement.

Sex Hormone Binding Globulin: The Testosterone Trap

In the circulation, testosterone is tightly bound to sex hormone binding globulin (SHBG), weakly bound to albumin, and a small percentage is unbound (free). Testosterone bound to SHBG is unavailable to enter peripheral cells and is functionally trapped in a nonactive form. SHBG is a testosterone trap. Only the unbound and albumin-bound forms of testosterone can enter cells and be converted to the potent androgen DHT, thereby stimulating androgen effects. In normally cycling, well-estrogenized women, SHBG concentrations are remarkably high, trapping most of the circulating testosterone. In hyperandrogenic women, SHBG levels are remarkably low, allowing the testosterone to freely enter cells and be converted to DHT. Obesity and insulin resistance independently contribute to a decrease in SHBG concentration. Measurement of SHBG is a reasonable proxy for identifying hyperandrogenic women and can be used in conjunction with total testosterone to calculate a "free androgen index."

Obesity Is Associated With Increased Circulating Androgens and Decreased Sex Hormone Binding Globulin

Obesity and insulin resistance cause a dual defect in androgen biology, increasing testosterone production and reducing SHBG concentrations resulting in an additive increase in free testosterone, which is then available to be converted to DHT in peripheral tissues.[3] Obesity is associated with insulin resistance in muscle, liver, and adipose tissues, resulting in a compensatory hyperinsulinemia. Insulin stimulates ovarian production of androgens and reduces SHBG synthesis by the liver.

Cigarette Smoking Is Associated With Increased Circulating Androgens

Constituents of cigarette smoke—nicotine and anabasine—and their metabolites, including cotinine, disrupt the delicate balance of adrenal cortisol and androgen production by increasing ACTH production and by inhibiting the 21-hydroxylase enzyme, resulting in more androgen production for every molecule of cortisol produced. Women of all ages are susceptible to this effect. Women who smoke have approximately 15% greater androgen levels than women who do not smoke.[4]

Suppressing Luteinizing Hormone Secretion Decreases Circulating Androgens

As noted earlier, the dual defect in gonadotropins—excess LH and insufficient FSH—results in an imbalance in the ovarian follicle causing excess androstenedione production and insufficient estrogen production resulting in a hyperandrogenic state. Any treatment that lowers LH production will result in a decrease in ovarian androgen production. In parallel, any treatment that increases FSH production or action can overcome the relative LH excess and convert the excess androgen to estrogen, often restoring a normal estrogen environment to the follicle, allowing it to grow and ovulate.

HYPERANDROGENISM: REPRODUCTIVE AND METABOLIC ABNORMALITIES

Most hyperandrogenic women have both reproductive and metabolic abnormalities. The reproductive abnormalities include the following: (a) Excess LH and insufficient FSH secretion, caused in part by an excess secretion of hypothalamic gonadotropin-releasing hormone (GnRH). (b) Excess ovarian production of androgen and insufficient ovarian production of estradiol. (c) Stunted growth of ovarian follicles resulting in follicles in the range of 2 to 9 mm in diameter. (d) In the absence of a large, 18- to 25-mm healthy preovulatory follicle, the estradiol surge and the LH surge cannot occur resulting in oligo- or anovulation. (e) The excess ovarian androgen secretion results in decreased SHBG, increased free testosterone, increased testosterone entry into peripheral cells, and excessive conversion of testosterone to DHT, the most potent intracellular androgen. This causes hirsutism and in some women other signs of androgen excess, such as alopecia. (f) The oligo- and anovulation of hyperandrogenism can cause anovulatory infertility.

The metabolic abnormalities of hyperandrogenic women include the following: (a) Insulin resistance in both lean and obese hyperandrogenic women in muscle, liver, and adipose tissue. Insulin resistance is typically more severe in obese hyperandrogenic women. (b) An increased prevalence of impaired glucose tolerance, impaired fasting glucose, and diabetes. (c) An increased prevalence of gestational diabetes if pregnancy occurs. (d) An increased prevalence of the metabolic syndrome, especially in obese hyperandrogenic women. The phenotype of the metabolic syndrome includes decreased levels of high-density lipoprotein cholesterol (HDL-C), increased fasting triglycerides, increased fasting glucose (greater than 100 mg/dL), increased waist circumference and hypertension. (e) Evidence for endothelial inflammation and accelerated atherosclerosis.

The pathophysiology of insulin resistance associated with hyperandrogenism is not well characterized. Disorders of oxidative phosphorylation, insulin receptor defects, and intracellular postreceptor defects in insulin signaling may all contribute. In hyperandrogenic women, the ovarian theca appears to be stimulated by insulin to produce androstenedione and testosterone. Consequently, hyperinsulinemia caused by insulin resistance conspires with elevated LH levels to cause excessive ovarian androgen secretion.

HYPERANDROGENISM: DIFFERENTIAL DIAGNOSIS

The main causes of hyperandrogenism are (a) the PCOS, (b) idiopathic hirsutism, (c) NCAH due to 21-hydroxylase deficiency, (d) adrenal and ovarian androgen-secreting tumors, and (e) other endocrine causes of hyperandrogenism including Cushing disease or acromegaly. In large case series, the relative frequency of these four causes of hyperandrogenism are 80% PCOS, 15% idiopathic hirsutism, 4% NCAH and less than 1% adrenal and ovarian tumors, and less than 1% Cushing disease or acromegaly.

Currently, there are three competing approaches to the diagnosis of PCOS (Table 3.1). The author uses the National Institutes of Health (NIH) consensus criteria that require the presence of BOTH hyperandrogenism and oligo- or anovulation as manifested by oligomenorrhea or amenorrhea.[5] Imaging studies to document the polycystic ovary morphology are not required in this diagnostic system. Hyperandrogenism must be present.

The Rotterdam criteria require the presence of two of three findings: hyperandrogenism, oligo- or anovulation, or an imaging study indicating a polycystic ovary morphology.[6] To consistently use the Rotterdam criteria, all women undergoing a diagnostic evaluation for hyperandrogenism need high-resolution sonography of the ovaries. This results in an increase in resource use with little evidence for clinical benefit. Also, the Rotterdam criteria permit the diagnosis of PCOS even if the woman is not hyperandrogenic, but hyperandrogenism is the sine qua non of PCOS. The Rotterdam criteria results in a higher prevalence of PCOS than the NIH consensus criteria because of its relaxed diagnostic criteria.

The criteria of the Androgen Excess Society *requires* the presence of hyperandrogenism but allows for the use of either oligo-ovulation *or* a polycystic ovary morphology as evidence of ovarian dysfunction.[7]

Idiopathic hirsutism is diagnosed when the patient self-reports excess facial hair growth, but she has regular ovulatory menstrual cycles. It is likely that many women with idiopathic hirsutism have a subtle increase in ovarian, adrenal, and/or hair follicle androgen production. A few may have a mild form of PCOS and would meet the Rotterdam criteria. However, if a woman has regular ovulatory cycles, it is unlikely that she has a significant endocrinopathy.

NCAH due to 21-hydroxylase deficiency has a phenotype that is identical to the phenotype of PCOS: hyperandrogenism and oligo-ovulation are uniformly present. Consequently, the only method to identify NCAH due to 21-hydroxylase deficiency is to measure an early morning 17-hydroxyprogesterone level, which is always elevated in NCAH and never elevated in PCOS.

Ovarian and adrenal tumors usually present with marked elevation in circulating total testosterone (greater than 150 ng/dL and often greater than 200 ng/dL) and signs of virilization including deepening of the voice register, increased upper body muscle mass, clitoromegaly, and/or alopecia. The screening test for Cushing disease is a 24-hour urine cortisol measurement. A screening test for acromegaly is measurement of circulating insulin-like growth factor-1 (IGF-1).

DIAGNOSIS OF HYPERANDROGENISM

Self-Reported Hirsutism

Historically, hirsutism was assessed using the modified Ferriman-Gallwey scoring system that uses nine separate body sites, each scored 1 to 4 and summed to a single total number to measure the severity of hirsutism. The Endocrine Society now recommends that clinicians focus their attention on the patient's self-report of hirsutism, rather than a quantitative assessment of hirsutism on physical examination.

TABLE 3.1 Three Approaches to the Diagnosis of the Polycystic Ovary Syndrome

Criteria	NIH Consensus Criteria	Rotterdam (ESHRE-ASRM) Criteria Two of Three Criteria Below Required for Diagnosis	Androgen Excess Society Criteria
Hyperandrogenism (clinical diagnosis or laboratory evidence)	Required	Not required	Required
Ovarian dysfunction	Oligomenorrhea or Amenorrhea required	Oligomenorrhea or Amenorrhea	Oligomenorrhea or Amenorrhea or polycystic ovary morphology on ultrasound
Ovarian imaging	Not required	Polycystic ovary morphology on ultrasound	

The author uses the National Institutes of Health (NIH) consensus criteria because it can be used without the use of any laboratory or imaging studies. For all three diagnostic approaches, other causes of androgen excess, such as NCAH or ovarian or adrenal tumors, should be excluded if clinically indicated. The Rotterdam criteria for PCOS are met if two of the following three are present: hyperandrogenism, oligomenorrhea or amenorrhea, or polycystic ovary morphology on ultrasound. The Rotterdam criteria for a polycystic ovary morphology are 12 or more follicles 2 to 9 mm in diameter on each ovary or an ovarian volume greater than 10 mL.

Status of Menstrual Cycles

Women with PCOS typically report irregular menstrual cycles starting in adolescence. Many never have regular ovulatory cycles. Women with idiopathic hirsutism always have regular ovulatory cycles. Women with ovarian or adrenal androgen-secreting tumors are typically amenorrheic.

Physical Examination

Key points in the physical examination of hyperandrogenic women are presented in Table 3.2.

Laboratory Issues

Key laboratory tests are outlined in Table 3.2.

Total and Free Testosterone

Either total or free testosterone or both can be measured. Serum testosterone provides the best laboratory estimate of the severity of androgen overproduction. Total testosterone measurement is performed by all clinical laboratories and is a reasonably well-standardized test, especially in the range greater than 1.5 ng/mL. The measurement of total testosterone is usually less expensive than free testosterone measurement. Many women with PCOS have a total testosterone level in the upper end of the normal range (about 0.60 to 0.80 ng/mL). This range is not well standardized among clinical laboratories. If the total testosterone level is greater than 2 ng/mL (200 ng/dL), the patient probably has ovarian stromal hyperthecosis or an adrenal or ovarian tumor

TABLE 3.2 Key Physical Examination Findings and Clinically Useful Laboratory Tests for the Evaluation of Women With Polycystic Ovary Syndrome

Physical Examination

Finding	Cutoff	Purpose
Blood pressure	130/85 mm Hg for metabolic syndrome	Women with PCOS are at increased risk for hypertension.
Body mass index	Obesity, >30 kg/m^2	Women with PCOS have an average BMI of 30–35 kg/m^2. Treatment for obesity is warranted if detected.
Waist circumference	>34.6 inches	Obese women with increased waist circumference (apple shape) have more visceral adipose tissue and greater metabolic derangements than obese women with thinner waists (pear shape).
Waist-to-hip ratio	>0.85	A waist-to-hip ratio >0.85 is associated with increased visceral fat; see waist circumference section above.
Ferriman–Gallwey hirsutism score	>8	May indicate the presence of hyperandrogenism
Acne	Any	
Clitoromegaly Increased upper body muscle mass		Signs of virilization that may indicate the presence of an ovarian or adrenal tumor
Alopecia Deepening of voice register	Male pattern	
Acanthosis nigricans or skin tags	Any	May indicate the presence of insulin resistance

Laboratory Tests

Test	Interpretation	Purpose
Total testosterone	>0.6 ng/mL	Consistent with hyperandrogenism
	>2.0 ng/mL	May be associated with ovarian hyperthecosis or adrenal or ovarian tumors
Early morning 17-hydroxyprogesterone	>2.0 ng/mL	Evidence for the presence of NCAH caused by 21-hydroxylase deficiency
High-density lipoprotein cholesterol (HDL-C)	<50 mg/mL	Consistent with insulin resistance and hyperandrogenism
Fasting triglycerides	>150 mg/dL	
Fasting glucose	>100 mg/dL	Consistent with insulin resistance and/or pancreatic β-cell dysfunction
Hemoglobin A_{1C}	>6%	Warrants further testing for impaired glucose tolerance or frank diabetes. Levels below 6% are unlikely to be associated with clinically significant diabetes.

PCOS, polycystic ovary syndrome; BMI, body mass index; NCAH, nonclassical adrenal hyperplasia.

and needs a detailed evaluation, which should include imaging studies of the ovary and adrenal glands. The free testosterone measurement is more sensitive in detecting mild androgen overproduction. The free testosterone assay is not well standardized among laboratories and is more expensive than a total testosterone assay. The author does not usually order free testosterone measurements.

17-Hydroxyprogesterone

Approximately 4% of women who present with hyperandrogenism and oligo-ovulation or anovulation have NCAH resulting from a 21-hydroxylase deficiency. The prevalence of this genetic disorder varies markedly among different ethnic groups, from below 1% in Hispanic populations to as high as 8% in Ashkenazi Jewish populations and even higher in Eskimo populations. The decision to screen for the disorder depends on the cost-benefit assessment of detection and the baseline prevalence of the disorder in the patient's ethnic group. If the 17-hydroxyprogesterone level at 8 AM is greater than 2 ng/mL, the patient probably has NCAH resulting from a 21-hydroxylase deficiency. This diagnosis can be confirmed by a 60-minute ACTH stimulation test. The test uses a form of synthetic ACTH (cosyntropin) that contains the first 24 of the 39 amino acids of natural ACTH; 0.25 mg is given intravenously or intramuscularly, and the 17-hydroxyprogesterone level is measured 60 minutes later. A post-ACTH 17-hydroxyprogesterone level greater than 10 ng/mL confirms the diagnosis of NCAH resulting from a 21-hydroxylase deficiency.

Dehydroepiandrosterone Sulfate

DHEA-S, an androgen prohormone that can be converted to testosterone in the periphery, is secreted almost exclusively by the adrenal glands. The normal DHEA-S level in premenopausal women is 0.12 to 5.35 mcg/dL. A DHEA-S level above 10.70 mcg/dL—that is, more than twice the upper limit of normal—should raise concern for a possible adrenal tumor.

Prolactin, Thyroid-Stimulating Hormone, and Follicle-Stimulating Hormone

If the patient has amenorrhea, the laboratory workup should include an assessment of serum prolactin level to rule out a prolactin-secreting pituitary tumor. In an amenorrheic woman, most clinicians also routinely measure serum FSH and thyroid-stimulating hormone (TSH) levels.

Luteinizing Hormone and Follicle-Stimulating Hormone

The measurement of serum LH presents a special problem in the laboratory evaluation of PCOS. In the research setting—using multiple serum LH measurements (every 10 minutes for at least 8 hours) and a precise and reliable LH assay—elevated LH levels can be documented in more than 95% of women with PCOS. However, because LH secretion is pulsatile and the standard commercial assays are not as precise as research assays, measurement of LH in clinical practice is of little use. An elevated LH level is reasonably specific for PCOS, provided the sample was not taken during a preovulatory LH surge. A normal LH value does not necessarily exclude PCOS, however, because the test sample may have been drawn when the patient was at the nadir of an LH pulse. Another important point is that as body mass index (BMI) increases, the normal range for LH decreases.[8] Nomograms that control serum LH for BMI are not widely available. Many women with PCOS have an LH:FSH ratio greater than 2. The ratio of LH:FSH may be a better test for PCOS than a single LH measurement. The author does not usually order serum LH or FSH in evaluating women for hyperandrogenism.

Serum Anti-Müllerian Hormone

Anti-Müllerian hormone (AMH) concentration is elevated two-fold to three-fold in the circulation of women with PCOS compared with ovulatory women. The number of small antral follicles detected on transvaginal imaging is correlated with serum AMH concentration. Some authorities have recommended replacing the Rotterdam criteria of counting the number of small antral follicles with a serum measurement of AMH.[9]

Imaging Issues

Demonstration of polycystic ovaries on pelvic ultrasonography is not essential for the diagnosis of PCOS using the NIH consensus criteria but is necessary if using the Rotterdam criteria. The Rotterdam criteria for diagnosing a polycystic ovary morphology are 12 or more follicles 2 to 9 mm in diameter on each ovary or an ovarian volume greater than 10 mL. Measuring small follicles accurately usually requires transvaginal imaging. Virginal adolescents and young women may not accept a transvaginal imaging study. Pelvic imaging is always clinically indicated if the ovaries are palpably enlarged on physical examination or the total testosterone concentration is greater than 2.0 ng/mL.

Diagnosis of Diabetes

The American Diabetes Association recommends screening for type 2 diabetes in women with PCOS.[10] In a population of women with PCOS, approximately 4% have undiagnosed diabetes and 23% have impaired glucose tolerance. There are no clear national guidelines about how to best screen and test for diabetes mellitus in women with PCOS. Data suggests that the oral glucose tolerance test may be more sensitive than the

TABLE 3.3 Definition of the Metabolic Syndrome in Women

Criteria	NCEP	IDF
Required	None	Waist circumference >31 in
Number of additional abnormalities required	≥3	≥2
Fasting glucose	≥100 mg/dL	≥100 mg/dL
HDL cholesterol	<50 mg/dL	<50 mg/dL
Fasting triglyceride	≥150 mg/dL	≥150 mg/dL
Waist circumference	34.6 in	See earlier.
Blood pressure	≥130/85 mm Hg	≥130/85 mm Hg

From the National Cholesterol Education Program (NCEP) and International Diabetes Federation (IDF). Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735; Alberti KG, Zimmet P, Shaw J. The metabolic syndrome: a new worldwide definition. *Lancet*. 2005;366:1059.

fasting glucose or hemoglobin A_{1c} ($HgbA_{1c}$) for detecting diabetes in women with PCOS. In one study of 254 women with PCOS who had both a fasting blood glucose and a 75-g oral glucose tolerance test, 3.2% had diabetes based on the fasting blood glucose and 7.5% had diabetes based on the oral glucose tolerance test.[11] Similar findings have been reported in adolescents.[12] The Rotterdam consensus conference recommended screening all *obese* women with PCOS with an oral glucose tolerance test. Most cases of undiagnosed diabetes occur in the obese women with PCOS, not lean women with PCOS. Many authorities are using measurement of $HgbA_{1c}$ as a screening test for diabetes. An $HgbA_{1c}$ greater than 6% should prompt further testing with an oral glucose challenge.

Diagnosis of the Metabolic Syndrome

The diagnosis of metabolic syndrome is presented in Table 3.3. The diagnosis of the metabolic syndrome requires laboratory testing for HDL-C (abnormal, less than 50 mg/dL) and fasting glucose (greater than 100 mg/dL) and triglycerides (abnormal, greater than 150 mg/dL).[13,14]

Detecting Insulin Resistance

At least 50% of women with PCOS have significant insulin resistance and hyperinsulinemia. There is no consensus on how to detect insulin resistance using laboratory methods, and most inexpensive methods are not sensitive. The Rotterdam consensus conference concluded that testing for insulin resistance is not warranted. They recommended that clinicians focus their efforts on detecting and treating the key elements of the metabolic syndrome.

TREATMENT OF HYPERANDROGENISM

The treatment of hyperandrogenism generally focuses on the following key concerns: (a) oligomenorrhea, (b) hirsutism, (c) anovulatory infertility, (d) prevention of endometrial hyperplasia, (e) obesity, (f) metabolic syndrome, and (g) prevention of diabetes. The treatment approach to these issues, including first-line and alternative therapies, are presented in Table 3.4 and discussed in more detail in the following sections.

TABLE 3.4 Therapeutic Options for the Treatment of Oligomenorrhea, Hirsutism, and Anovulatory Infertility and Protection Against Endometrial Hyperplasia in Hyperandrogenic Women With Polycystic Ovary Syndrome and Idiopathic Hirsutism

Chief Compliant	First-Line Therapy	Alternative 1	Alternative 2
Oligomenorrhea	Estrogen-progestin cyclic contraceptive	Cyclic progestin withdrawal	Metformin
Hirsutism	Estrogen-progestin cyclic contraceptive without an antiandrogen for the first 6 months of therapy. If response is suboptimal, add an antiandrogen (spironolactone).	Shaving, waxing, depilatories, electrolysis, laser treatment, or eflornithine	Spironolactone monotherapy (ensure that pregnancy cannot occur)
Anovulatory infertility	Weight loss	Clomiphene	Metformin or aromatase inhibitors
Protection against endometrial hyperplasia	Estrogen-progestin cyclic contraceptive	Cyclic progestin withdrawal	

Therapeutic Options for the Treatment of Obesity and Metabolic Syndrome and Prevention of Diabetes in Hyperandrogenic Women With Polycystic Ovary Syndrome

Chief Compliant	First-Line Therapy	Alternative 1	Alternative 2
Obesity	Low-calorie diet and increased exercise	Bariatric surgery	Weight loss drugs: sibutramine, orlistat
Metabolic syndrome	Low-calorie diet and increased exercise	Metformin	Target treatment to the lipid, glucose, or blood pressure abnormality
Prevention of diabetes	Low-calorie diet and increased exercise	Metformin	Pioglitazone, rosiglitazone

Hirsutism

There is little data from clinical trials to guide the treatment of hirsutism, and most recommendations are based on expert opinion. Most authorities believe that treatment decisions for hirsutism should be largely based on the patient's assessment of her need for treatment, balanced with an objective assessment of the severity of her hirsutism and hyperandrogenism.

Mechanical, Chemical, and Electrical Methods and Light Therapy for the Treatment of Hirsutism

Plucking hair either one hair at a time, or en masse, by waxing is an inexpensive approach to hair removal that results in the temporary absence of hair at the site for 4 to 8 weeks. Shaving is effective but only removes hair to just below the surface of the skin, so it must be repeated daily. Shaving can produce skin irritation because of microabrasions or the preparations used on the skin to facilitate the smooth motion of the blade. The use of a chemical depilatory, such as a thioglycolate, to disrupt disulfide bonds in the hair protein, results in the gelatinization of the hair, and it can then be wiped or scraped away. Depilation usually results in the temporary absence of hair at the site for about 2 weeks.[15]

Electrolysis is a technique where a fine needle electrode is inserted into the base of the hair follicle and an electric current is activated to destroy the living cells in the hair matrix and follicle. Electrolysis can result in the permanent destruction of hair follicles, but many factors including placement of the electrode and magnitude of electric energy applied may cause variable results, with some hairs regrowing. Electrolysis is time consuming and can be painful.

Lasers and noncoherent pulsed light therapies can generate sufficient heat at the base of the hair follicle to cause the destruction of the hair follicle. Melanin in the hair bulb is an ideal target for laser treatment in light-skinned women. Using a 694 nm ruby laser, about two-thirds of patients report greater than 50% reduction in hair density following a single treatment. With multiple treatments, more than 90% of patients will report greater than 50% reduction in hair density. Lasers with a wavelength of 1064 nm (Nd:YAG) or 755 nm (alexandrite) can effectively destroy hair follicles in women with dark skin pigment without excess skin damage. Patients typically need four to six treatments over a 6-week period to achieve optimal results.[16] Paradoxically, laser light treatment appears to occasionally provoke greater growth of terminal hair in nearby untreated areas and the growth of vellus hair (hypertrichosis) in the treated area.[17]

Eflornithine for the Treatment of Hirsutism

Eflornithine 13.9% cream is applied daily to the face in areas where hair growth is bothersome. Hair growth is usually reduced within 4 to 6 weeks of initiation of treatment. When treatment is discontinued, hair typically grows back. Eflornithine can be associated with reddening of the skin and an acneiform reaction. Eflornithine can be combined with laser therapy[18] or endocrine therapy for a more rapid clinical response.

Acne

Most cases of acne vulgaris are caused by follicular hyperproliferation, androgen-stimulated sebum production, colonization with *Propionibacterium acnes*, and inflammation. For hyperandrogenic women, treatment of acne should be multimodal and include (a) an estrogen-progestin contraceptive, (b) a topical retinoid, (c) a topical antibiotic, and (d) benzoyl peroxide. The combination of a topical antibiotic plus benzoyl peroxide is more effective than either agent used alone.[19] Pregnant women should not be treated with synthetic retinoids, either topical or oral.

Endocrine Therapy of Hyperandrogenism: Hirsutism and Oligomenorrhea

Estrogen-Progestin Treatment

For most women with hyperandrogenism, elevated concentrations of LH cause the stroma and theca cells of the ovarian follicles to synthesize excessive androstenedione and testosterone. In turn, excess production of androgens stimulates hair growth resulting in hirsutism and stunts the development of ovarian follicles resulting in oligo-ovulation and oligomenorrhea. In these hyperandrogenic women, elevated LH production can be best suppressed with an estrogen-progestin contraceptive, either a pill, vaginal ring, or patch.[20] In addition to suppressing pituitary LH and ovarian androgen production, estrogen-progestin contraceptives have additional benefits in the treatment of hyperandrogenism: (a) They increase liver production of SHBG, thereby reducing free testosterone concentration; (b) the progestin in the contraceptive prevents the development of endometrial hyperplasia and cancer; and (c) through mechanisms that are not fully delineated, they reduce adrenal androgen production, thereby lowering DHEA-S levels. These beneficial effects of the estrogen-progestin contraceptive will reduce hair growth and result in regular uterine withdrawal bleeding in most hyperandrogenic women.

All estrogen-progestin contraceptives contain the synthetic estrogen, ethinyl estradiol, and a synthetic progestin. The pharmacology of the available synthetic progestins varies. For example, some progestins are mildly androgenic (norgestrel) and others are antiandrogenic (drospirenone). However, the clinical impact of these minor pharmacologic differences is not sufficiently strong to warrant using one progestin over another. Any estrogen-progestin contraceptive can be effective in the treatment of hirsutism and oligomenorrhea. Many authorities use a formulation with a 30 to 35 mcg ethinyl

estradiol dose and a progestin from the norethindrone family.

Antiandrogen Treatment

If estrogen-progestin treatment does not result in satisfactory reduction of hair growth after 6 months, an antiandrogen should be added to the regimen. In comparative clinical trials, spironolactone 100 mg daily, finasteride 5 mg daily, and flutamide 250 mg daily all have similar efficacy in the treatment of hirsutism.[21] Spironolactone and flutamide are antiandrogens and block androgen action at the androgen receptor. Finasteride is a 5α-reductase inhibitor and blocks the conversion of testosterone to DHT. None of these drugs are formally approved for the treatment of hirsutism. Drug labeling warns all women to not take finasteride or flutamide. Consequently, spironolactone is the most commonly used antiandrogen. Spironolactone doses between 50 and 200 mg are effective.[22] A standard dose of 100 mg daily is effective in most women. Spironolactone and its active metabolites have long half-lives. It may be taken as a single dose once daily. Spironolactone should not be prescribed to women with renal insufficiency because it can cause hyperkalemia in these patients.

Insulin Sensitizers

Metformin, rosiglitazone, and pioglitazone have been studied for the treatment of hyperandrogenism and insulin resistance in women. In general, when used to treat women with hyperandrogenism and oligo-ovulation, these agents are associated with restoration of ovulatory menses in more than 50% of subjects and a reduction in serum testosterone and insulin.[23,24] However, meta-analysis of clinical trials concludes that metformin is not particularly effective for the treatment of hirsutism but is effective for the treatment of oligomenorrhea in some women.[20] Rosiglitazone is only modestly effective for the treatment of hirsutism.[25]

Glucocorticoids—Avoid Using for the Treatment of Hirsutism

Treatment of hyperandrogenic women with exogenous glucocorticoid decreases pituitary secretion of ACTH and suppresses adrenal secretion of androstenedione and DHEA-S. For women with NCAH, treatment with exogenous glucocorticoids will suppress ACTH and adrenal androgen secretion and improve hirsutism and may be associated with the induction of regular menses. However, in some studies, estrogen-progestin contraceptives plus an antiandrogen were more effective than glucocorticoids in the treatment of hirsutism in women with NCAH. Given the potential adverse effects of chronic glucocorticoid treatment, including weight gain, osteopenia, glucose intolerance, and adrenal suppression, the Endocrine Society recommends against their use for the treatment of hirsutism.

Gonadotropin-Releasing Hormone Analogues—Expensive and Effective

GnRH analogues, used alone or in combination with estrogen-progestin contraceptives, are effective in suppressing LH and decreasing ovarian androgen production.[26,27] For women with severe ovarian hyperandrogenism, such as those with ovarian stromal hyperthecosis who do not respond adequately to estrogen-progestin contraceptives, combination treatment with a GnRH analogue plus an estrogen-progestin contraceptive may be effective. Women with hyperandrogenism with contraindications to the use of estrogen-progestin contraceptives, including women with factor V Leiden mutations who have an increased risk for deep venous thrombosis, are excellent candidates for GnRH analogue monotherapy. A commonly used regimen is leuprolide acetate depot 3.75 mg intramuscular injection every 4 weeks.

Combination Estrogen-Progestin Plus an Antiandrogen Plus an Insulin Sensitizer

European investigators have reported that the use of an estrogen-progestin contraceptive may be associated with an increase in visceral fat but not overall body mass in adolescents and young hyperandrogenic women. To prevent the increase in visceral fat, they recommend combination treatment with an estrogen-progestin contraceptive PLUS an antiandrogen PLUS an insulin sensitizer.[28] In one case series, they have reported the successful use of an estrogen-progestin contraceptive PLUS an antiandrogen PLUS TWO insulin sensitizers, metformin plus pioglitazone. Until large-scale head-to-head clinical trials are reported, these multidrug regimens are best considered as experimental.

Anovulatory Infertility

For hyperandrogenic women with anovulatory infertility, a graded approach with increasing use of more resource intensive treatment is warranted. This approach includes the use of (a) weight loss, (b) clomiphene, (c) low-dose FSH injections, (d) ovarian drilling, and (e) in vitro fertilization-embryo transfer (IVF-ET).[29]

Weight Loss

There are no large-scale trials of weight loss as a fertility treatment for hyperandrogenic women with anovulatory infertility. However, small placebo-controlled trials and uncontrolled intervention trials report that weight loss is often effective in restoring ovulation in hyperandrogenic women with anovulatory infertility. Weight loss in the range of 10% of body mass may be effective.[30,31] Weight loss is very effective in the treatment

of hyperandrogenism in obese women, but it is very difficult to achieve.

Clomiphene Versus Metformin

Both clomiphene and metformin are effective for ovulation induction in hyperandrogenic women, but in a large clinical trial, clomiphene resulted in a significantly greater ovulation rate and live birth rate than metformin. Clomiphene is the agent of choice for ovulation induction in hyperandrogenic anovulatory women. In a large trial sponsored by the NIH, 626 hyperandrogenic women with ovulatory infertility were randomized to clomiphene alone, metformin alone, or clomiphene plus metformin.

The live birth rate was 23, 7, and 27%, respectively. Clomiphene was clearly superior to metformin for the treatment of infertility in this population, except that clomiphene was associated with more twin and triplet pregnancies than metformin.[32]

The FDA-approved doses for clomiphene are 50 or 100 mg daily for a maximum of 5 days per cycle. After a spontaneous menses or the induction of menses with a progestin withdrawal (medroxyprogesterone acetate 10 mg orally daily for 5 days), clomiphene (50 mg daily for 5 days) is started on cycle day 3, 4, or 5. In properly selected women, 50% will ovulate through the use of this clomiphene regimen. Another 25% will ovulate if the dose of clomiphene is increased to 100 mg daily. During each cycle, determination of ovulation should be attempted by the use of urine LH testing or luteal phase progesterone measurements. Additional tests to monitor ovulation include basal body temperature charts, measurement of urine estrone glucuronide and pregnanediol glucuronide and ultrasound monitoring of follicle growth and rupture. In most women, ovulation occurs approximately 5 to 12 days after the last dose of clomiphene. Measurement of the urinary LH surge is recommended to assist the patient in prospectively determining the periovulatory interval. The LH surge, which occurs about 36 hours before ovulation, can be monitored by daily testing for a surge in urine LH concentration using an over-the-counter home LH assay kit.

For women who do not ovulate on standard doses of clomiphene, 2 months of suppressing LH by using a combination estrogen-progestin may reduce circulating androgens and increase the ovulation rate with standard doses of clomiphene. For example, in one study, hyperandrogenic women who had not ovulated in response to standard doses of clomiphene were randomized to a 42-day course of estrogen-progestin (Desogen) followed by clomiphene 100 mg daily for cycle days 5 to 9 or to the clomiphene alone. When a ripe follicle was observed by ultrasound, human chorionic gonadotropin (hCG) 10,000 units was injected to initiate ovulation. The estrogen-progestin regimen suppressed circulating testosterone by about 50%. The ovulation rates for the estrogen-progestin-clomiphene regimen versus the clomiphene-only regimen was approximately 71% versus 8%.[33] Other studies have also reported that elevated concentrations of circulating testosterone may reduce the efficacy of clomiphene in inducing ovulation.[34]

Aromatase Inhibitors

The aromatase inhibitors letrozole and anastrozole are effective for induction of ovulation in hyperandrogenic women but are not approved for this purpose. In one trial, letrozole 2.5 mg daily for 5 days and anastrozole 1 mg daily for 5 days resulted in a pregnancy rate of 12 and 15% per cycle, respectively, in women with PCOS who did not ovulate with clomiphene treatment.[35]

Follicle-Stimulating Hormone and Ovarian Drilling

In women with PCOS, induction of ovulation with long-term, low-dose FSH treatment appears to result in a high pregnancy rate with a low rate of complications such as high-order multiple gestation and ovarian hyperstimulation.[36] In this approach, 75 units of FSH are given daily for the first 14 days; the dose is then raised by 37.5 units every 7 days until follicular ripening is complete. The "go slow, go low" approach extends the number of days of FSH injections required, potentially frustrating the patient, but it reduces the likelihood of excessive follicle development and the associated risks of multiple gestation and ovarian hyperstimulation syndrome.

Laparoscopic drilling of the ovary is the most widely studied surgical treatment for ovulation in PCOS; approximately 1000 cases have been reported, although no controlled studies have been undertaken.[37] These reports demonstrate that surgery to induce ovulation causes a decrease in circulating LH (50% decline) and testosterone (30% decline) and an increase in FSH (30% increase). The pregnancy rate is in the range of 50% at 12 months and 70% at 24 months. The surgical techniques used for ovarian drilling vary between centers. However, all use a laser or electrosurgery to make multiple millimeter-size punctures in each ovary.

In one randomized study, 50 women with PCOS and anovulatory infertility were randomized to ovarian surgery for ovulation induction or injections of FSH. At 6 months, the cumulative pregnancy rate was 28% in the surgical group and 33% in the FSH injection group (no significant difference).[38] A meta-analysis of six trials concluded that ovarian surgery and FSH injections had similar efficacy for ovulation induction in women with PCOS. The long-term effects of ovarian surgery on ovarian function were not well characterized.[39]

In Vitro Fertilization-Embryo Transfer

IVF-ET has been demonstrated to be effective in the treatment of infertile women with PCOS who fail to become pregnant with gonadotropin injections. In preliminary reports, IVF-ET treatment of infertile women with

PCOS has been associated with a per-cycle live birth rate of 25 to 35%.[40]

Obesity

The American College of Physicians recommends that the treatment of obesity include (a) the foundation of all obesity treatment programs is counseling about diet, lifestyle, exercise, and goals for weight loss; (b) use of pharmacologic options for those individuals who have not achieved weight loss with diet and exercise, including sibutramine, orlistat, phentermine, or diethylpropion; and (c) bariatric surgery may be an option for women with a BMI greater than 40 kg/m^2 who have failed diet and exercise and who have obesity-related diseases such as diabetes, hypertension, sleep apnea, or dyslipidemia.[41] Other authorities will offer bariatric surgery to women with a BMI greater than 35 kg/m^2 who have obesity-related diseases such as diabetes, hypertension, sleep apnea, or dyslipidemia.

Pharmacologic Treatment of Obesity

The two agents most commonly used to treat obesity are sibutramine and orlistat. Sibutramine is an inhibitor of norepinephrine, serotonin, and dopamine reuptake into nerve terminals. Doses between 5 and 15 mg daily are approved for weight loss. These doses are associated with a 5 to 10% decrease in body mass.[42] Sibutramine increases blood pressure on average by 2 mm Hg and pulse by 5 bpm. However, with effective weight loss, blood pressure will ultimately decrease. Sibutramine is metabolized by cytochrome P450 systems and is relatively contraindicated in women taking ketoconazole. Orlistat inhibits pancreatic lipases, thereby decreasing intestinal absorption of fats, and fetal fat excretion is increased. The recommended dose is 120 mg three times daily. An over-the-counter formulation of 60 mg is also available. With the 120-mg three times daily dose, weight loss averages in the range of 5 to 10%. Orlistat has been demonstrated to be effective in reducing weight in women with PCOS.[43]

Metformin treatment is also associated with weight loss. In the Diabetes Prevention Program, after 3 years of follow-up, patients treated with metformin lost on average 2.5% of their body weight.[44] In obese hyperandrogenic women, treatment with metformin for 2 years was not associated with changes in body mass but did reduce fasting glucose, insulin, and testosterone and increased SHBG.[45]

Bariatric Surgery

Bariatric ("baro" is Greek for "weight") surgery is an effective treatment for severe obesity, and the number of bariatric procedures performed annually is increasing. Bariatric surgery is an effective approach to the treatment of diabetes in overweight men and women.[46] Bariatric surgery is also successful in the treatment of the obesity, anovulation, hirsutism, and insulin resistance associated with PCOS. For example, in one cohort study, 24 severely obese women with PCOS and a mean age of 34 years were treated with Roux-en-Y gastric bypass. The initial BMI was 50 kg/m^2. The women were followed for a mean of 28 months. The mean excess weight loss 12 months following surgery was 57%. All 24 women resumed normal menses, and 77% of the women reported improvement in their hirsutism.[47] Similar results have been reported in another small cohort.[48] For women with PCOS and long-standing severe obesity, there is a low probability that diet and exercise will result in normalization of BMI. For these women, bariatric surgery is a reasonable treatment alternative. Following bariatric surgery, pregnancy should be delayed until the patient reaches a stable weight, typically 12 to 18 months after surgery.[49]

Gestational Diabetes

Women with PCOS who become pregnant are at increased risk for gestational diabetes. Prior to ovulation induction, these women should attempt to achieve an optimal metabolic state. If obese when they achieve pregnancy, they should be screened early in pregnancy for gestational diabetes mellitus (GDM) and treated using standard protocols. If an oral antihyperglycemic agent is used, glyburide may be more effective than metformin.[50]

Following delivery, women with PCOS who had GDM during pregnancy are at increased risk of developing type 2 diabetes mellitus (T2D). A clinical trial has reported that the risk of developing T2D is reduced by either lifestyle changes (weight reduction 7% of body mass and exercise 150 minutes weekly) or by treatment with metformin (850 mg twice daily).[51]

UNIQUE CLINICAL SITUATIONS ASSOCIATED WITH HYPERANDROGENISM

Adolescents With Oligomenorrhea: Functional Oligomenorrhea or Evidence of Polycystic Ovary Syndrome?

There are no established criteria for the diagnosis of PCOS in young adolescents because regular menses may not be expected in this age group. Most adolescents establish a regular pattern of menstrual cycles by age 16 years. When adolescents age 16 years or older presents with severe oligomenorrhea, they must be evaluated for causes of secondary amenorrhea with measurement of prolactin, TSH, and FSH, and evaluation for hyperandrogenism. Many hyperandrogenic adolescents will not yet have hirsutism because too little time has elapsed between the onset of hyperandrogenism and the hair follicle response to slightly elevated androgens, so measurement of serum testosterone and DHEA is warranted. If the androgens are elevated, it is likely that the adolescent is at increased risk for developing the full PCOS phenotype.[52]

Ovarian Stomal Hyperthecosis

Hyperthecosis refers to the presence of nests of luteinized theca cells that are secreting androstenedione and testosterone in the ovarian stroma. Unlike the cells in ovarian tumors, the nests of theca cells remain responsive to LH stimulation, and complete suppression of LH will decrease androgen production. Compared to women with PCOS, women with ovarian hyperthecosis have an increased prevalence of severe hirsutism and virilization. Most women with ovarian hyperthecosis have a total testosterone greater than 2 ng/mL. Magnetic resonance imaging may detect hyperintense T2-weighted images in the ovarian stroma that mark the activated luteinized theca cells.[53] For women who have completed their family, laparoscopic bilateral oophorectomy is an effective treatment for hyperthecosis. For women who wish to preserve their ovaries, estrogen-progestin contraceptive alone or with a GnRH analogue may be effective.

Postmenopausal Woman With Hirsutism

No data from clinical trials is available to guide the treatment of hirsutism in postmenopausal women. Hormone therapy with a low-dose estrogen-progestin plus an antiandrogen is recommended by some endocrine authorities. A combination of estradiol 1 mg and drospirenone 0.5 mg (Angeliq) plus spironolactone will reduce LH, likely decrease androgen production; increase SHBG production, thereby reducing free testosterone; and block androgen action in the hair follicle, thereby benefiting the hirsutism.

Alopecia

For many hyperandrogenic women, the development of alopecia is especially concerning to their self-image and sense of well-being. Hyperandrogenic alopecia is especially difficult to treat. There are few clinical trials upon which to base treatment. The author recommends combined treatment with an estrogen-progestin contraceptive, spironolactone, and a topical antiandrogen such as minoxidil 5%.

Valproic Acid Treatment

Epilepsy and bipolar disorder can be associated with oligomenorrhea and hirsutism. Treatment with valproic acid appears to be associated with an increased prevalence of PCOS previously discussed that present for the underlying condition. Valproic acid increases both pituitary secretion of LH and ovarian secretion of testosterone.[54] This may result in the onset of oligomenorrhea and hirsutism in many women.

Racial, Ethnic, and Geographic Variation in the Clinical Presentation of Polycystic Ovarian Syndrome

Ethnic, racial, and other population factors may influence the phenotype and prevalence of PCOS. In a large cohort study from Kaiser Permanente, the prevalence of PCOS among women age 25 to 34 years was 2.6%. Women with PCOS were more likely to be obese and have dyslipidemia and diabetes. Among the PCOS cohort, Blacks and Hispanics were more likely than Whites to be obese. Asians with PCOS were less likely to be obese than Whites. Among the PCOS cohort, Blacks were more likely and Hispanics less likely to have hypertension than Whites. Asians and Hispanics were more likely to have diabetes than Whites.[55] In another study, Mexican American women with PCOS were reported to have higher BMI and fasting insulin than Caucasian women with PCOS.[56] The risk of PCOS varies among countries. The prevalence of PCOS in Greece (6.8%) and the Southeast United States (6.6%)[57] appears to be greater than the prevalence in Finland (3.5%).[58] Populations with a low BMI and a low prevalence of diabetes are probably at reduced risk for developing PCOS.

CLINICAL NOTES

- *Estrogen-progestin treatment is the key treatment for most hyperandrogenic women.* For most hyperandrogenic women with hirsutism and oligomenorrhea, an estrogen-progestin contraceptive is effective because it lowers pituitary secretion of LH, thereby decreasing ovarian and adrenal secretion of androgens, reducing circulating androgens, and producing withdrawal uterine bleeding.
- *Antiandrogens, such as spironolactone, are effective for the treatment of hirsutism.* For hyperandrogenic women with hirsutism who do not have sufficient relief of their excessive hair growth after 6 months of estrogen-progestin treatment, an antiandrogen such as spironolactone 100 mg daily should be added to the regimen.
- *Hirsutism and alopecia are the major concerns of many women with hyperandrogenism.* Hirsutism can also be treated with plucking and waxing, chemical depilatories, shaving, electrolysis, laser light, and eflornithine. Alopecia requires multimodal therapy and is difficult to treat.
- *Clomiphene is the key treatment for most hyperandrogenic women with anovulatory infertility.* For hyperandrogenic women with anovulatory infertility,

(continues)

an orderly approach to treatment involves the use of sequentially more resource intensive interventions. The treatment sequence includes (a) weight loss if the woman is obese, (b) clomiphene, (c) low-dose FSH injections, (d) ovarian drilling, and (e) IVF-ET.

- *Obesity is at the root of many cases of hyperandrogenism.* Many women with PCOS are obese, and treatment should focus on lifestyle changes for weight reduction. Bariatric surgery is an option for women with morbid obesity who do not achieve sufficient reduction.
- *Lifestyle changes and metformin are key interventions for hyperandrogenic women with metabolic dysfunction.* Many women with PCOS are at increased risk for diabetes. For women at increased risk of developing diabetes, lifestyle changes (weight loss in the range of 10% and 150 minutes of exercise weekly) reduce the risk. Metformin 850 mg twice daily also reduces the risk of developing diabetes.

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CHAPTER 4

Vulvovaginitis

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The Centers for Disease Control and Prevention (CDC) defines vaginitis as a disorder commonly presenting with vaginal discharge and/or vulvar itching and irritation, with or without the presence of vaginal odor. These symptoms may be caused by infections of the urogenital tract, contact dermatitis, hormonal changes, systemic diseases with dermatologic manifestations, and neuropathies of different origins. Women commonly assume the cause of their symptoms to be yeast infections or contact allergies, which prompt them to self-treat or seek medical advice. Bacterial vaginosis, trichomoniasis, and candidiasis are the most common causes of vaginal discharge. In bacterial vaginosis, the normal vaginal flora is replaced by an excess of anaerobic microorganisms, mycoplasmas, and *Gardnerella vaginalis*. Vaginal discharge may also be caused by cervicitis.[1] This chapter covers the most common causes of vulvovaginitis.

NORMAL VAGINAL FLORA

Identification techniques for independent bacteria in the means of culture have revolutionized the study of microorganisms in the vaginal ecosystem. The use of amplification, cloning techniques and subsequent analysis of sequences of bacterial genes (genes that codify for bacterial rRNA 16 S) in samples of vaginal fluid have allowed the identification of the majority of common species of lactobacilli and other microorganisms. Thus, these techniques have demonstrated that *Lactobacillus* spp. do not always correspond to the dominant species in the vagina of healthy women.[2,3]

A variety of hydrogen peroxide—H_2O_2 and non-H_2O_2—producing *Lactobacillus* spp. and other organisms such as *Streptococcus* spp. can maintain proper vaginal pH between 3.8 and 4.5 and microbial equilibrium in healthy women.[4] Acid pH prevents the excessive proliferation of potentially pathogenic microorganisms. There are racial differences in the normal composition of the vaginal flora, as well as the concentration and behavior of particular vaginal microbes, suggesting a role for human and bacterial genetic variations.[5]

The composition of the vaginal flora is not constant; there are variations in response to exogenous and endogenous factors. These factors include the menstrual cycle, pregnancy, hormonal contraception, frequency of sexual intercourse, use of douching or deodorant products, and use of antibiotics and/or other medications with immunosuppressive properties.

BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) is defined as a clinical syndrome resulting from an alteration of the microbial ecosystem of the vagina. It is classified as a vaginosis, instead of a vaginitis, because it is limited to the epithelium, without tissue infection. It is often considered to be the most common cause of abnormal vaginal discharge in the United States, with some studies suggesting a prevalence of almost 30%, and it has emerged as a global problem contributing to the HIV epidemic.[6,7] Unfortunately, even after proper treatment, the risk of recurrence is high, with 30 to 50% of patients relapsing within 2 to 3 months.

Risk Factors

Risk factors for BV include new or multiple sexual partners if condoms or other barrier methods are not used, increasing douching frequency, spermicide use, intravaginal foreign bodies or products, history of a female sexual partner, other sexually transmitted diseases, low income, low educational attainment, increasing body mass index, and decreasing general health status.[6,8–10] Cigarette smoking increases the risk for BV by suppressing the growth of hydrogen peroxide–producing lactobacilli.[11] Women who have never been sexually active can also be affected. The risk of BV may be lower among women who use oral contraceptive pills.[12] It is more common in African American women than in other ethnic groups, but the prevalence among Latinas is significantly higher than among Whites.[13]

The epidemiologic profile of BV corresponds to a sexually transmitted disease. BV is associated with several sexual behaviors; it is less common among women who consistently use condoms during intercourse and is also less frequent among those whose male partner are circumcised. However, significant debate exists about its sexual transmission because it has been found in women who have never had sex; it is difficult to isolate BV-associated organisms from the male genital tract, and partner treatment does not appear to prevent recurrences.[14]

Etiology

In BV, a marked decrease in lactobacilli that produce hydrogen peroxide (H_2O_2) is associated with a massive overgrowth of *G. vaginalis* and other anaerobic bacteria such as *Atopobium vaginae*, *Prevotella* spp., *Mobiluncus* spp., and *Mycoplasma hominis*.[1] *A. vaginae*, in particular, appears to be dependent on *G. vaginalis* for the colonization of the vaginal epithelium, and their concurrent presence is highly specific for BV and seems associated with treatment failure and BV recurrence.[15,16] *Mobiluncus* spp. also seems highly specific for BV, found merely when BV is present, although only in 50% of the cases.[17]

Using fluorescent rDNA-targeted probes, researchers have identified a complete or partial biofilm adherent to epithelial cells in vaginal biopsies of women with BV. In women without BV, the vaginal mucosa is mostly covered with *Lactobacillus* spp. growing unorganized, but in women with BV almost consistently appears a dense biofilm composed of 60 to 95% *G. vaginalis* and 1 to 40% *A. vaginae*. The characteristic "clue cells"—squamous vaginal epithelial cells covered with *G. vaginalis*—are actually small fragments of the biofilm following desquamation.[15]

Interestingly, certain strains of *G. vaginalis* may be unable or unlikely to cause disease, whereas others are better suited to elicit disease. Strains that fail to elicit BV may not be able to adhere to, or form a biofilm on, the vaginal epithelium as avidly as strains that cause BV. Also, BV- and non-BV–associated strains of *G. vaginalis* have significant genetic differences.[18] On the other hand, studies of the biofilm-forming potential and cytotoxic activity of *G. vaginalis* have shown that of several BV-associated anaerobes, only *G. vaginalis* possesses both properties.[19] If indeed *G. vaginalis* is more virulent than other BV-associated anaerobes and those having relatively low virulence, other BV-associated anaerobes may be opportunists that colonize the vagina after a biofilm-forming strain of *G. vaginalis* has invaded the vaginal epithelium.

Although many consider BV as a polymicrobial infection, and BV is a condition characterized by remarkable bacterial diversity, recent evidence suggests that the presence of *G. vaginalis* could be the essential element. It is also likely that *A. vaginae* and *G. vaginalis* are the decisive pathologic basis of BV.[15]

BV appears strongly related to host immunity and microbial virulence. For example, some women produce *G. vaginalis*–specific IgA that gives them immune defense against BV, whereas in others, vaginal bacteria may produce sialidase and enzymes that attenuate this protective factor.[20]

Genetic predisposition could play an important factor in the etiology of BV. Recognition of microorganisms by the innate immune system is the trigger for a successful antimicrobial defense. Heat shock protein 70 (hsp70) and mannose-binding lectin (MBL) are two transmembrane proteins of the innate immunity system. In patients with BV, a decrease in hsp70 production or release and/or inadequate MBL function may inhibit the innate immune response, facilitating the anaerobic overgrowth. Several genes codify the production of these proteins. Carriage of some polymorphisms of those genes is associated with instability and/or malfunction of the aforementioned innate immune system, thus rendering basis for a hypothesis of a genetically determined immunity that is altered in women with BV.[21]

Complications of Bacterial Vaginosis

BV has been linked to gynecologic opportunistic infections with BV-associated bacteria and infections due to sexually transmitted agents (Table 4.1). Opportunistic ascending genital tract infections include postabortion and postpartum endometritis, pelvic inflammatory disease (PID), and vaginal cuff infection after hysterectomy.

Pregnancy complications including first-trimester miscarriage, late fetal loss, premature rupture of membranes, preterm labor, and preterm births, especially in women with history of preterm deliveries.[1,22–24]

The alteration of the local flora characteristic of BV diminishes colonization resistance, increasing the risk of acquiring *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, HSV-2, and HIV-1. In addition, BV increases viral replication and vaginal shedding of the HIV-1 and HSV-2 viruses, accelerating the spread of these infections.[25] BV also appears to be associated with uterine cervical human papilloma virus (HPV) infection[26] and with subfertility.[27] Because of its possible association with vaginal cuff infection after hysterectomy and with postabortion endometritis, screening and treatment before these procedures may be beneficial.[28]

Diagnosis of Bacterial Vaginosis

The most common presenting symptoms of BV are foul-smelling, homogenous, clear, white or gray discharge, often more apparent and odorous when vaginal alkalinity increases after intercourse exposure to semen or

TABLE 4.1 Complications of Bacterial Vaginosis

Gynecologic	Pregnancy
Post abortion and postpartum endometritis	First trimester miscarriage
PID	Late fetal loss
Vaginal cuff cellulitis after hysterectomy	Premature rupture of membranes
Increased risk of acquiring *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*	Preterm labor

PID, pelvic inflammatory disease.

TABLE 4.2 Diagnostic Features of Vulvovaginitis

Feature	Normal	Bacterial Vaginosis	Candidal Vaginitis	Trichomonas Vaginitis
Symptoms	None or physiologic discharge	Thin, malodorous, white/gray discharge	Pruritus, white thick or watery discharge, vulva soreness	Profuse, offensive discharge, dyspareunia
Discharge	White or clear, variable minimal to no odor	Moderate, adherent, white to gray, homogenous	White, scant to moderate, varying from milky to cottage cheese-like	Profuse, yellowish, homogenous, frothy
Exam	Normal	No inflammation	Introital, vaginal, and vulvar erythema; exfoliations from scratching	Erythema and swelling of vulvar and vaginal wall; "strawberry" cervix
pH of vaginal fluid	<4.5	>4.5	<4.5	5–6.0
Amine (whiff) test	Negative	Positive	Negative	Occasionally positive
Saline microscopy	Normal epithelial cells and lactobacilli (long rods)	Clue cells, absence of leukocytes, decreased lactobacilli	Normal flora	Increased leukocytes, motile trichomonads, no clue cells or abnormal flora
10% KOH microscopy	Negative	Negative	Hyphae and budding yeast	Negative

KOH, potassium hydroxide.

during the menses, in the absence of signs of inflammation. Nevertheless, more than half of the women with BV could be asymptomatic.[29] Given the unspecific or absent symptoms, clinical suspicion of BV or vaginitis warrants a laboratory study to reach a definitive diagnosis.

Clinical Diagnosis (see Table 4.2)

The clinical diagnosis of BV is made if three or more of the following Amsel criteria are present:

- Thin, adherent, and homogenous grayish-white vaginal discharge
- Vaginal pH higher than 4.5
- The presence of more than 20% or more clue cells of the total of epithelial cells on saline wet mount. Clue cells are vaginal epithelial cells with borders obscured by a heavy coating of adherent coccobacilli (*G. vaginalis* and other anaerobic bacteria).
- A fishy amine odor before or after adding potassium hydroxide at 10% to a wet mount slide ("whiff" test)

Although the appearance and odor of the discharge are subjective criteria, a pH greater than 4.5 is the most sensitive indicator, whereas the presence of clue cells is considered the single most specific indicator of BV.[30,31] Despite the development of more sensitive and specific laboratory test, cost and practicality make the Amsel criteria the best in-office way to diagnose BV. Cultures are not used in its diagnosis because they include bacteria normally present in the vagina.[1] The Pap test can be used to detect clue cells and BV flora, but its sensitivity is lowered by observer bias.[20]

Gram Stain–Based Diagnosis

The Nugent Gram stain score is a diagnostic alternative with higher sensitivity than the Amsel criteria. Vaginal fluid or discharge is collected on a glass slide, stained in the laboratory, and examined under oil immersion for the presence of lactobacilli, *Gardnerella*, and *Mobiluncus* morphotypes. A Nugent Gram score of 7 or higher indicates flora corresponding to BV.[31] A score of 4 to 6 is indicative of intermediate vaginal microflora, and a score of 0 to 3 is considered normal. Although an intermediate score does not constitute BV, it seems to be linked to a range of complications. Despite concerns about different collection techniques, the way the specimen is spread on the glass slide, and the use of different fixation methods and time, the Nugent Gram is highly reliable and accurate and is commonly considered the current gold standard.

The alternative *Ison Score* of Gram-stained vaginal fluid uses grade I (normal flora), *Lactobacillus* morphotype only; grade II (intermediate flora), reduced *Lactobacillus* morphotype with mixed bacterial morphotypes; grade III (BV), mixed bacterial morphotypes with few or absent *Lactobacillus* morphotypes. Two grades have been added: grade 0, epithelial cells with no bacteria seen and grade IV, epithelial cells covered with Gram-positive cocci only.[32] Some clinicians find useful for its more complete characterization of the vaginal flora, and because the test is easier and faster, although it has shown low interobserver reliability.

Point-of-Care Commercial Tests

A series of tests has been developed and are commercially available to assist in the diagnosis of BV in an office setting.

- A rapid chromogenic test to detect sialidase enzyme–producing flora (BV Blue) is a useful point-of-care diagnostic tool to provide a presumptive diagnosis of BV, especially in situations where microscopic capabilities are unavailable. BV Blue has shown good sensitivity, specificity, and positive and negative predictive value, compared to Amsel criteria and Nugent Gram stain.[33–35]

- FemExam is a point-of-care test card that determines pH and triethylamine levels in vaginal fluid, but it does not seem to have significant benefits over the Amsel criteria and the Nugent Gram slide.[36,37] The CDC does not recommend its use because of its low sensitivity and specificity.[1]
- The so called electronic nose (Electronic Sensor Array) is used to detect volatile organic amino acids in vaginal fluid is also sued at point-of care. It has shown a sensitivity and specificity of about 80% compared to the Amsel criteria and Gram-stain diagnosis.[38–40]
- Pip Activity Testcard is a test to detect proline iminopeptidase activity of anaerobic flora in vaginal discharge, especially *G. vaginalis*. It was developed in the 1990s, and it appears to have high diagnostic accuracy.[1,41]
- DNA probes of *G. vaginalis*, *T. vaginalis*, and *Candida* spp. are available as office procedures that can detect concentrations higher than 2×10^5 bacterial cells per mL of vaginal fluid.[30] The Affirm VP III (Becton Dickenson, San Jose, California) is commercially available and can be performed in less than 45 minutes, although it is usually better done in the laboratory.
- Office dipstick tests to measure pH show good correlation of increased pH with BV (88% sensitivity), but they lack specificity (58%) because other vaginal pathologies can also increase the pH. A self-test pH globe containing acidity indicator paper is commercially available. Women can monitor their vaginal pH by inserting in their vagina one finger cover with the globe. Because pH is a sensitive indicator of BV, the test has been widely used in screening programs to prevent preterm births in Europe. Pregnant women are instructed to seek medical care if the globe indicates a pH greater than 4.7.[30,31,37]

Molecular Diagnosis of Bacterial Vaginosis

Molecular diagnosis of BV is an important diagnostic alternative to make the study of BV more precise and overcome the reliability problems of Gram stain diagnosis. Polymerase chain reaction (PCR) methods have shed light on the bacterial microflora of the vagina, showing that bacteria from the Clostridials order (BVAB 1–3) as well as *Atopobium*, *Snethea/Leptotrichia*, *Megasphaera* 1 and 2, and a TM7 bacterium, are highly specific for BV, and therefore can be used to assist in its diagnosis and treatment follow-up. Several conventional PCR assays were available for sensitive study of the vaginal flora, but despite their high sensitivity, these tests did not gain widespread use. Recent studies of vaginal bacteria using qualitative real-time polymerase chain reaction (QRT-PCR) in individuals with different presentations of BV and different responses to treatment, suggest that distinct BV profiles—different combinations of vaginal bacteria—might predispose to different health outcomes.[42–44] Once large cohort studies validate the use of QRT-PCR, newly available methods will allow a more precise diagnosis of BV, and more importantly, the detection of women at risk by determining bacterial profiles that predispose them to develop BV.

Treatment of Bacterial Vaginosis

The primary objective of treating BV is to resolve or alleviate the presenting symptoms. Although BV may resolve spontaneously, treating it, even in asymptomatic patients, helps prevent common associated complications such as *C. trachomatis* or *N. gonorrhoeae*, HIV, and other sexually transmitted diseases (STDs). In addition, BV tends to be a recurring problem, thus treatment should also aim at reducing recurrences. Treatment modalities include antibiotics, antiseptics and disinfectants, acidifying agents, and probiotics.

Bacterial Vaginosis Treatment With Antibiotics

Topical or oral metronidazole and clindamycin are currently the drugs of choice (Table 4.3). Both medications seem to be equally effective either orally or topical.[1,44,45] The most appropriate treatment depends on the patient preference and lifestyle, possible side effects, drug interactions, and other associated infections and comorbidities. The recommended regimens are as follows:

- Metronidazole 500 mg orally, twice a day for 7 days, or
- Metronidazole gel (0.75%), one full applicator (5 g) intravaginally, or
- Clindamycin cream (2%), one full applicator (5 g) intravaginally at bedtime for 7 days

TABLE 4.3 Treatment

Antibiotic	Dose	Time
Oral metronidazole	500 mg twice a day	7 days
Topical metronidazole gel 0.75%	Full applicator 5 g intravaginally	7 days
Topical clindamycin cream 2%	Full applicator 5 g intravaginally	7 days
Alternative regimes		
Oral tinidazole	2 g once a day	2 days
Oral tinidazole	1 g once a day	5 days
Oral clindamycin	500 mg twice a day	7 days
Topical clindamycin ovules	1 g ovule once a day intravaginally	3 days
Antiseptics	Chlorhexidine Hydrogen peroxide Povidone iodine Benzydamine Dequalinium chloride Polyhexamethylene biguanide	No data
Probiotics	Lactobacilli	Promising data

Other effective regimens include the following:

- Oral tinidazole either 2 g once a day for 2 days, or 1 g a day for 5 days, or
- Clindamycin 500 mg orally twice a day for 7 days, or 100 mg ovules intravaginally once a day at bedtime for 3 days

Oral metronidazole 750-mg extended release tablets once daily for 7 days is an alternative treatment. A single dose of clindamycin intravaginal cream is another treatment under consideration.[44]

Resistance of BV-associated anaerobes to antimicrobials is troublesome. Studies have shown different levels of resistance to metronidazole, but this seems to be of less concern than resistance to clindamycin. Anaerobic bacteria seem more likely to develop resistance to clindamycin, raising concern because macrolides are widely used in obstetrics and gynecology.

Patients should be advised to avoid sexual intercourse during treatment, or to use condoms consistently.[1] However, clindamycin creams are oil-based and may damage condoms and diaphragms, thus complete abstinence is recommended when choosing it as treatment. Treating partners has no effect on the patient's response to therapy or risk of relapse, thus it is not recommended. Douching is not advised either, because it does not alleviate the symptoms or the bacterial unbalance and increases the risk of relapse. In addition, patients must be cautioned to avoid alcohol during and 24 hours after treatment with oral metronidazole or tinidazole.

Treatment With Antiseptics and Disinfectants

Antiseptics have a broad spectrum, usually disrupting the bacterial cell membrane, and usually do not cause antimicrobial resistance. They are usually gentle on the vaginal mucosa when used in appropriate concentrations. Antiseptics are a valuable alternative in the treatment of BV, especially when systemic or local antibiotics are better avoided because of the patient's condition or choice. The most commonly used antiseptics are chlorhexidine, hydrogen peroxide, povidone iodine, benzydamine, dequalinium chloride, and polyhexamethylene biguanide. Treatment efficacy is similar among the different antiseptics available in the market. Use of povidone iodine for the treatment of BV in very young patients and in pregnant or nursing women should be avoided because of potential suppression of thyroid hormone production due to vaginal absorption of iodine.[44,46,47]

Use of Probiotics and Acidifying Agents

Probiotics are beneficial live microorganisms such as lactobacilli, bifidobacteria, and yeasts, among others.[48] Despite the folk use of fermented milk products for the treatment of BV, scientific evidence does not support claims to its effectiveness.[49] However, a few probiotic strains of lactobacilli show promising inhibitory or antagonistic activity against microorganisms associated with BV. On the other hand, the use of acidifying or buffering agents (e.g., acetic acid–based gel, lactate-buffered gel, acid-buffering gel, intravaginal vitamin C) has not shown significant effect in BV, but it is a promising approach as the delivery of acid-buffering agents onto the vaginal mucosa is perfected.[44]

Assessing Treatment Efficacy

If the diagnosis was made using the Amsel criteria, treatment efficacy can be assessed by the resolution of the symptoms and signs that led to the diagnosis. If the diagnosis was made using the Nugent score, practitioners may consider it cured if the score is less than 7, indicating a return to intermediate microflora and the likely disappearance of symptoms. However, intermediate microflora is significantly more likely to cause BV recurrences, and many use more strict Nugent scores of less than 3 as an indication of the return to normal microflora.

Recurrences

As mentioned before, recurrence of BV may occur in more than 30% of women within 3 months. Risk factors associated with recurrence include prior history of BV, having a female sex partner, and keeping the same partner since the prior infection. In addition, the presence of *A. vaginae*, which is often resistant to metronidazole, in conjunction with *G. vaginalis*, is correlated with higher rates of treatment failure and recurrence.[50] Apparently, the persistence of the *G. vaginalis* and *A. vaginae* biofilm after treatment is associated with relapse, even though the bacteria are metabolically less active (slow growth) and the symptoms may temporarily recede.[16] Leaving untreated other specific bacteria, such as *Mobiluncus* spp., may also contribute to the high rate of recurrence in BV.[17] Follow-up treatment for the prevention of BV recurrence with metronidazole gel at 0.75% twice weekly for 16 weeks alone or in conjunction with intravaginal boric acid is potentially beneficial. On the other hand, clindamycin reduces vaginal *Mobiluncus* morphotypes to a greater extent than metronidazole in patients with BV, which seems to correlate with a higher BV cure rate.[17]

VULVOVAGINAL CANDIDIASIS

Vulvovaginal candidiasis (VVC) is a common cause of acute vaginitis. It is responsible for 17 to 39% of all cases of vaginitis, second only to BV.[51] Approximately 75% of women will experience at least one episode of candidal vulvovaginitis during their lifetime.[52] Although VVC is usually not a serious medical condition, the impact includes bothersome symptoms, psychological stress,

and hundreds of millions of dollars annually in medical evaluations and treatments.

Pathophysiology

Candida albicans is responsible for the 85 to 95% of *Candida* infections. Other less common causes of VVC include *Candida glabrata*, *Candida parapsilosis*, and *Candida tropicalis*.[53] Some studies have suggested that the frequency of non-albicans species is increasing.[54] VVC is not considered an opportunistic infection. Although VVC is not traditionally considered a sexually transmitted disease, there does appear to be some relation to sexual activity.[55] Sexual partners of women with symptomatic infection are four times more likely to be colonized than partners of unaffected women, and colonization is often of the same strain in both partners.[56,57]

C. albicans can be a part of the normal vaginal flora; it is found in 10 to 25% of asymptomatic women. The most likely source for vulvovaginal colonization is from the perianal area and rectum. The progression to symptomatic infection and inflammation is complex and not fully understood. Normal vaginal bacterial flora is probably the most important defense against colonization and symptomatic inflammation.[1,58] Both host inflammatory response to *Candida* invasion and yeast virulence factors contribute to the development of symptomatic disease.

Risk Factors

Most cases of candidal vulvovaginitis occur in women without identifiable cause. However, several risk factors for VVC have been identified (Table 4.4). Evaluating a woman for the presence of risk factors is important for treatment because some patients with risk factors are less likely to respond to a conventional short course of treatment.

Clinical Features

There is a spectrum of clinical presentations ranging from asymptomatic colonization to severely symptomatic. Women may report itching, burning, irritation, dyspareunia, burning with urination, and a whitish thick discharge.[51]

TABLE 4.4 Risk Factors for Vulvovaginal Candidiasis

Increased estrogen levels
Pregnancy
Estrogen therapy
Luteal phase of menstrual cycle
Immunosuppression
HIV infection
Corticosteroid use
Medical problems
Diabetes with poor glycemic control
Recent antibiotic use
Contraception
Use of high-dose oral contraceptives
Vaginal sponges, diaphragms
Intrauterine devices

Diagnosis

Multiple studies have shown that a reliable diagnosis of VVC cannot be made by history and physical exam alone. Studies have also demonstrated that even women with prior VVC often are not able to diagnose the cause of their vaginitis.[51,58]

On physical examination, excoriations may be present on the external genitalia. Vaginal pH is not altered in VVC. The discharge is classically a thick, adherent, "cottage cheese" discharge; however, some patients may have thin or no discharge.

Clinical suspicion for VVC should be confirmed with microscopic evaluation, and women with a positive result should receive treatment. For women with a negative wet mount who are symptomatic, vaginal cultures for *Candida* should be performed. Empiric therapy should be reserved until the cultures confirm the diagnosis. If *Candida* cultures are not available, empiric treatment should be considered. The definitive diagnosis of VVC can be made by either microscopic evaluation of vaginal fluid or a positive culture in a symptomatic woman (Table 4.5).

Culture should also be considered in cases of recurrent VVC, possible non-albicans, and in patients who fail to respond to therapy.

VVC can be further classified as uncomplicated or complicated disease. This classification is important because complicated VVC is more likely to fail standard treatment and therefore require more aggressive treatment.[51]

The diagnosis of VVC is further classified an uncomplicated or complicated infection (Table 4.6). Women with uncomplicated VVC can usually be successfully treated with a short course of antifungal treatment. Patients with complicated VVC may require more aggressive treatment.

Treatment

Uncomplicated candidiasis can be treated with a variety of topical and oral therapies (Table 4.7). Both topical and oral therapy results in 80 to 90% relief of symptoms and negative cultures. No agent is clearly superior in randomized trials. Over-the-counter therapy is available. As self-diagnosis is often unreliable; patients whose symptoms do not resolve should be instructed to seek care from a professional for evaluation.

TABLE 4.5 Diagnosis of Vulvovaginal Candidiasis

Blastospores or pseudohyphae on saline or KOH microscopy
or
Positive culture in a symptomatic woman

TABLE 4.6 Classification of Vulvovaginal Candidiasis

Uncomplicated
Sporadic or infrequent episodes
Mild to moderate symptoms or findings
Immunocompetent host
Candida albicans the likely pathogen
Nonpregnant
Complicated
Uncontrolled diabetes
Immunocompromised host
Debilitation
Severe symptoms or findings
Candida species other than *C. albicans*
Pregnancy
Recurrent VVC (≥4/year)

VVC, vulvovaginal candidiasis.

TABLE 4.7 Recommended Regimens for Uncomplicated Vulvovaginal Candidiasis

Over-the-counter intravaginal agents
Butoconazole 2% cream 5 g intravaginally for 3 days
Clotrimazole 1% cream 5 g intravaginally for 7–14 days
Clotrimazole 2% cream 5 g intravaginally for 3 days
Miconazole 2% cream 5 g intravaginally for 7 days
Miconazole 4% cream 5 g intravaginally for 3 days
Miconazole 100 mg vaginal suppository, one suppository for 7 days
Miconazole 200 mg vaginal suppository, one suppository for 3 days
Miconazole 1200 mg vaginal suppository, one suppository for 1 day
Tioconazole 6.5% ointment 5 g intravaginally in a single application
Prescription intravaginal agents
Butoconazole 2% cream (single dose bioadhesive product) 5 g intravaginally for 1 day
Nystatin 100,000 unit vaginal tablet, one tablet for 14 days
Terconazole 0.4% cream 5 g intravaginally for 7 days
Terconazole 0.8% cream 5 g intravaginally for 3 days
Terconazole 80 mg vaginal suppository, one suppository for 3 days
Oral agent
Fluconazole 150 mg oral tablet, one tablet in a single dose

The treatment of the CDC does not recommend use of fluconazole in pregnancy; 7 days of azole cream is recommended.[1,58]

Resistance of *C. albicans* to azole treatment is unusual. Non-albicans species are often azole resistant. Vaginal boric acid capsules have been shown to have 75% efficacy.[58]

In women with recurrent VVC, management approaches include treatment of each episode or prophylactic measures.[55,59]

There are over-the-counter therapies available. In general, these nonprescription antifungals have side effects and cure rates similar to prescription therapy. If a patient's symptoms do not resolve after one over-the-counter treatment regimen, he or she should seek care.[58]

TRICHOMONIASIS

Epidemiology

Trichomoniasis is a sexually transmitted disease caused by the bacterium *T. vaginalis*. Its annual incidence is estimated at 7.4 million cases in the United States,[51] however difficult to assess secondary to several reasons. First, *T. vaginalis* is often asymptomatic. Second, there are no screening guidelines, and third, it is not a reportable disease.[60] *T. vaginalis* is more prevalent in African American women (10.5%) compared to Caucasian women (1.2%). The prevalence is also more elevated in African American women age 14 to 19 years (8.3%) compared to other races of the same age group (1%).[60] Risk factors for prevalent *T. vaginalis* infection in adult women include poverty, lower educational level, concurrent chlamydial infection, non-Hispanic black race/ethnicity, history of multiple sexual partners, history of prior sexually transmitted infections, and history of substance abuse.[61] In female adolescents, risk factors include marijuana use, partner 5 or more years older, sex with nonsteady partner, and delinquency.[61]

Patients with trichomoniasis are also at increased risk of acquiring herpes. It is a common infection found among HIV-positive women with a prevalence of 11 to 30%.[62] It increases the risk of acquiring and transmitting HIV.[61]

Pathogenesis

T. vaginalis is a single-celled, pear-shaped protozoan, easily recognized on wet mount by its motile flagellae attached to the anterior aspect of the cell.[63] It is anaerobic and requires carbohydrate in the form of glycogen for energy, which is why it thrives in large quantities in the vagina.[63] This parasite adheres to the vaginal epithelial cells and releases cytotoxic substances causing epithelial breaks and inflammation, as well as increase in the vaginal pH.[60] The increase in HIV acquisition risk is thought to be due to an increase in the vaginal secretions of CD4 cells, which are targeted by the HIV virus.

Clinical Manifestations

As high as 50 to 75% of *Trichomonas* infections are thought to be asymptomatic.[64] When patients are symptomatic, however, the typical complaints include vaginal discharge, odor, and pain during intercourse and/or itching. Some women may complain of abnormal vaginal bleeding, or postcoital spotting, which results from the disruption of the vaginal and cervical epithelium. Upon examining the patient, signs raising suspicion for trichomoniasis are elevated vaginal pH, vaginal leukocytosis, vulvar erythema, frothy green discharge, and/or the "strawberry cervix" (colpitis macularis) described as punctuate hemorrhages on the cervix (<2% of culture-proven infections).[60] *T. vaginalis* may also infect the urethra leading to dysuria and frequency of micturition.

Diagnosis

Routine screening for trichomoniasis is not recommended. Diagnosis of *T. vaginalis* is usually performed by visualization of the motile trichomonads on wet mount under microscopy. A drop of vaginal discharge taken from the posterior fornix is added to a drop of normal saline onto a microscopic slide. This method has only 60 to 70% sensitivity and requires immediate evaluation of wet preparation slide for optimal results.[1] The gold standard for trichomoniasis diagnosis is culture with an 85% sensitivity and 100% specificity rate (most sensitive and specific commercially available diagnostic method). However, a culture requires a laboratory evaluation and up to 5 days for the final results. The culture is also too costly to be used as the primary method for diagnosis. In women who are suspected to have trichomoniasis (symptomatic) but with no observable mobile trichomonads on wet mount, culture is recommended.

In the past few years, there have been new tests developed to increase the sensitivity in detecting trichomoniasis: OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, Massachusetts), an immunochromatographic capillary flow dipstick technology and the Affirm VP III, a nucleic acid probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *C. albicans*.[1] These tests are both performed on vaginal secretions and have a sensitivity greater than 83% and a specificity greater than 97%. Both tests are point-of-care diagnostics. The results of the OSOM Trichomonas Rapid Test are available in approximately 10 minutes, and results of the Affirm VP III are available within 45 minutes. Although these tests tend to be more sensitive than vaginal wet preparation, false positives might occur especially in low-prevalence populations.[1,65]

Treatment

Symptomatic and asymptomatic trichomoniasis should be treated. Patient's sexual partners should also be treated. The standard treatment recommended by the CDC is metronidazole 2 g orally as a single dose or tinidazole 2 g orally as a single dose. An alternative regimen is metronidazole 500 mg twice daily for 7 days.[1] Women who are HIV positive receive the same treatment. Neither topical metronidazole therapy nor therapy with other topical classes of drugs has been shown to be as efficacious as oral therapy in the treatment of trichomoniasis.[64]

Women should be counseled about the potential disulfiram-like reaction (vomiting, palpitations, shortness of breath, and change in blood pressure) of these two medications when interacting with alcohol. Alcohol should therefore be avoided for 24 hours after metronidazole use and 72 hours after tinidazole use. Topical metronidazole may reduce symptoms but has high failure rates.

Pregnant Women

Trichomoniasis in pregnancy is associated with preterm delivery, premature rupture of membranes and low birth rate (independent of BV, also associated with preterm low birth weight).[66] Pregnant women with trichomoniasis have 30% higher risk of delivering preterm than those without the infection[64] and should be treated with the single 2 g dose of metronidazole. Eleven percent of preterm deliveries among African American women have been considered potentially attributable to trichomoniasis.[67] Many practitioners prefer to wait until after the first trimester to treat trichomoniasis in pregnancy, even though studies have not shown teratogenicity with metronidazole.[64]

There have not been any data supporting the treatment of asymptomatic pregnant women. On the contrary, treatment of asymptomatic women with metronidazole was ineffective in preventing preterm delivery and may have increased the risk as compared with the placebo group.[68] This phenomenon could be secondary to an inflammatory response caused by the dying trichomonads.[68,69] The CDC does not recommend treatment of asymptomatic pregnant women.[1]

Recurrent and Resistant Trichomoniasis

In patients believed to have resistant (estimated prevalence of 5%) or recurrent trichomoniasis, the practitioner should first rule out noncompliance to treatment or reinfection secondary to an untreated partner.

Some strains of *T. vaginalis* can have diminished susceptibility to metronidazole; however, infections caused by the majority of these organisms respond to tinidazole or higher doses of metronidazole (500 mg of metronidazole twice daily for 7 days). There are reports of effective treatment of resistant cases with high-dosage tinidazole, 500 mg four times a day for 14 days and even with 500 mg three times a day for 7 days.[51] Low-level metronidazole resistance has been identified in 2 to 5% of cases of vaginal trichomoniasis. High-level resistance is rare.[1] Tinidazole appears to have several advantages over metronidazole, including greater in vitro potency against both sensitive and resistant strains of *T. vaginalis*, a more prolonged duration of action, and improved patient tolerability.[70] If a higher dose of metronidazole or tinidazole regimen is still not effective, susceptibility testing of *T. vaginalis* to metronidazole and tinidazole should be performed to help guide therapy (Fig. 4.1).[71]

(MUCOPURULENT) CERVICITIS

The diagnosis of mucopurulent cervicitis is based on three findings visible: mucopurulent (yellow) cervical secretions, more than 10 polymorphonuclear leukocytes per high power microscope field (PMNL/HPF) in the cervical secretions, and friability at the external os (easily induced bleeding). Mucopurulent cervicitis has been associated

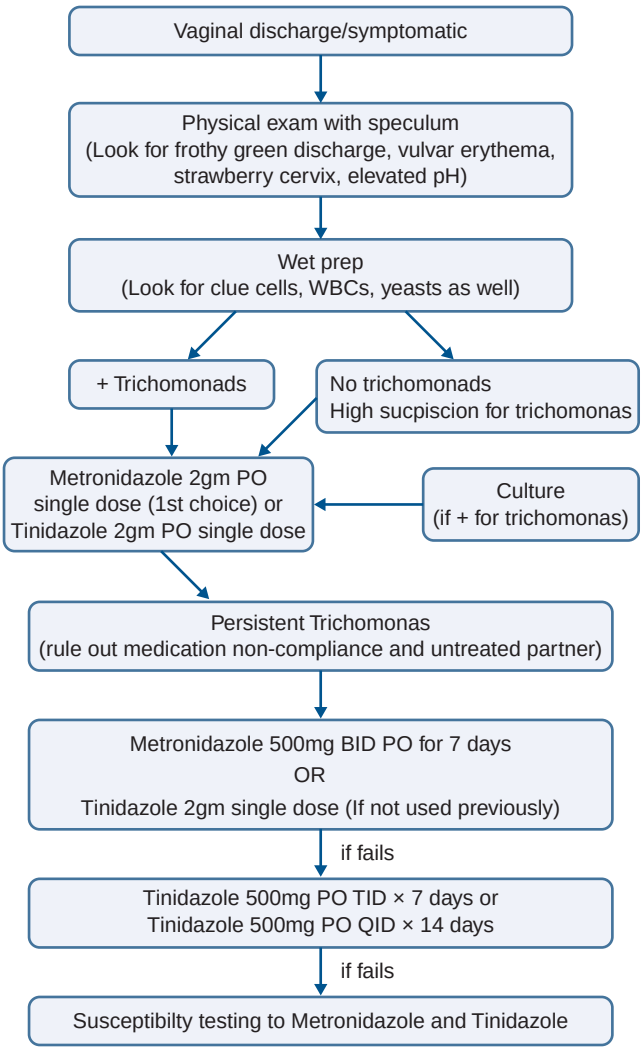

FIGURE 4.1 Trichomoniasis treatment guideline. (Data from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR*. 2010;59(RR-12):1–110; Schmid G, Narcisi E, Mosure D, et al. Prevalence of metronidazole-resistant Trichomonas vaginalis in a gynecology clinic. *J Reprod Med*. 2001;46:545–549.)

particularly with the presence of *C. trachomatis* but further studies have shown an association with *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *G. vaginalis*, *T. vaginalis*, and the clinical diagnosis of BV.[72–76]

Risk factors for cervicitis, included older age, less than 12 years of education, new male sex partner, female sex partner, and absence of vaginal H_2O_2-producing *Lactobacillus* species. No association with cervicitis was seen for current douching or smoking, race, time since or frequency of intercourse, or presence or quantity of vaginal bacteria other than H_2O_2-producing *Lactobacillus* species.[72,74–76]

Treatment recommendations are lacking, to date, we recommend oral doxycycline 100 mg twice a day for 10 days with metronidazole 500 mg orally twice a day for 7 days, extended 5-day regimens of azithromycin therapy increase cure rates to 96% after doxycycline treatment failure.[75–78]

PEDIATRIC VULVOVAGINITIS

The pediatric vulvo-vagina is particularly susceptible to problems because of the anatomy of the external genitalia, lack of estrogenization, and frequent contact with irritants. Symptoms and signs of vulvitis alone include pruritus, tenderness, dysuria, and erythema of the vulva (Fig. 4.2). The presence of discharge is more indicative of a vaginitis. The pathologic discharge associated with vaginitis should be distinguished from the physiologic clear, mucoid discharge that occurs during the newborn period and with the onset of pubertal development. The factors related to increased risk are the close proximity of vagina to the anus; the lack of labial fat pads and pubic hair; the thin, atrophic, non-estrogenized vaginal mucosa; the thin, delicate, vulvar skin; and an alkaline vaginal pH. The behavioral factors are tendency to poor hygiene, children's natural curiosity with exploration of their bodies including masturbation, and, in some, underlying chronic constipation.[79–82]

Differential Diagnosis

Vaginal foreign bodies, sexual abuse, sexually transmitted infections, pinworms, lichen sclerosus, psoriasis, eczema, contact dermatitis, scabies, lichen planus, ectopic ureter, congenital enteric fistula, and systemic disorders (e.g., Kawasaki disease, Crohn disease, scarlet fever)[80,83,84] and

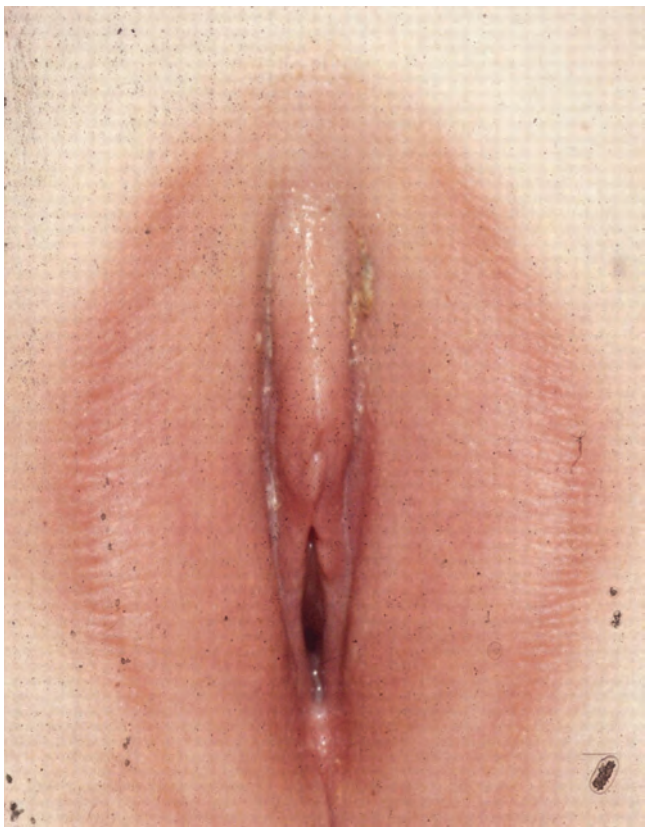

FIGURE 4.2 Pediatric vulvovaginitis.

nonspecific vulvovaginitis referred as vulvovaginal irritation without an identifiable bacterial pathogen, and it accounts for 74 to 80% of all cases.[81] It may also be referred to as irritant or atopic contact dermatitis.[82,85]

The non–sexually transmitted pathogens in vulvovaginitis are group A beta-hemolytic *Streptococcus*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Streptococcus pneumonia*, *Neisseria meningitides*, *Shigella*, and *Yersinia enterocolitica*.[81] Group A beta-hemolytic *Streptococci* and *H. influenzae*, transferred from the upper respiratory tract, are the two most common causative agents, in both primary care settings and referral populations.[79,80,82]

Successfully completing a gynecologic examination in the pediatric patient can be challenging for all parties involved: the patient, the caregiver, and the clinician. Prior to beginning the examination, it is important to explain it carefully to both the child and the parent or caregiver.[81] These young patients must be assured that the examination, although perhaps uncomfortable or embarrassing, will not be painful. The most common position used for genital examination is the frog-leg position.[82,85,86]

Treatment and Prevention

Treatment must be focused to treat any infection if found because the most common cause of vulvovaginitis in the pediatric population that is related to contact irritation is paramount to make some behavioral changes that will reduce the risk of develop vulvovaginitis.[81]

Children will need to avoid prolonged exposure to wet bathing suits, nylon clothing, and tight-fitting clothing (stockings, ballet leotards).[82,86]

The child can stand up to have her hair washed and rinsed so that she does not sit in the soapy water. The vulva should be dried with gentle patting of the vulvar skin or air-drying. When voiding, the child should urinate with her legs wide apart, and she should lean forward to minimize urine pooling in the lower vagina.[82,86]

In the setting of predominant perianal pruritus, nocturnal symptoms, and a low-grade vulvovaginitis, consider the diagnosis of pinworms (*Enterobius vermicularis*). Secondary infection with fecal organisms such as *Escherichia coli* is common with spread of the pinworms from the anus to the vagina.[85]

CLINICAL NOTES

- The normal vaginal pH is 3.8 to 4.5, there is minimal odor, and the phase of the menstrual cycle influences the quantity of normal discharge.
- All women with complaints of vulvovaginitis should have a directed history, physical examination, and in-office laboratory testing because symptoms alone are an insufficient basis for diagnosis and treatment.
- Office analysis of a woman with symptoms of vulvovaginitis includes a pH of vaginal secretions, an amine or whiff test, and wet mount using both saline and 10% KOH.
- BV is the most common cause of vaginosis among reproductive age women.
- BV can occur in women who have had a hysterectomy.
- Three of four clinical criteria must be met for the diagnosis of BV: milky, homogenous discharge; vaginal pH greater than 4.5, at least 20% of epithelial cells on wet mount are clue; and a positive whiff test.
- Approximately 50% of women with microbiologic evidence of BV are asymptomatic. Treatment of asymptomatic patients is not universally recommended.
- The therapy of choice for BV is metronidazole (Flagyl) 500 mg orally twice a day for 7 days. Alternative therapies include clindamycin 300 mg orally two times a day for 7 days, intravaginal metronidazole gel 0.75% 5 g intravaginally, or clindamycin cream 2% 5 g intravaginally.
- It is not currently recommended that sexual partners of women with BV undergo therapy, although some recommend this for women with intractable or recurrent disease.
- The risk of BV recurrence is high, with 30 to 50% of patients relapsing within 2 to 3 months.
- Twenty-five to 40% of women with positive vaginal cultures for *Candida* are asymptomatic. About 85 to 90% of yeast isolated from the vagina are *C. albicans* strains.
- Diagnosis of vaginal yeast infection is made by identification of hyphae or budding yeast in vaginal secretions mixed with 10% KOH solution and a normal vaginal pH.
- The presence of candidal vulvovaginitis in women who are menopausal or breast-feeding, or in prepubertal children, should raise suspicions of underlying diabetes mellitus.
- Up to 33% of patients with recurrent candidal vulvovaginitis (at least four mycologically proven symptomatic episodes of candidal vaginitis in a 12-month period with the exclusion of other pathogens) will have a non-albicans species present.

(continues)

- Of topical agents, the imidazole and triazole vaginal preparations are the best broad-spectrum antimycotics.
- Oral agents used for candidal vulvovaginitis, including ketoconazole 400 mg four times a day for 5 days, itraconazole 200 mg four times a day for 3 days or 400 mg as a single dose, or fluconazole 150 mg as a single dose, are all highly effective.
- The incidence of candidal vulvovaginitis is markedly increased in pregnant women. Vaginal therapy is recommended during pregnancy, not oral therapy.
- Women with recalcitrant candidal infection require long-term suppressive therapy. Treatment of the sexual partner does not seem to significantly reduce the recurrence rate.
- Trichomoniasis is a source of significant morbidity for women (e.g., atypical PID, cervical neoplasia, enhanced transmission or infection with HIV, preterm labor, postoperative infection).
- Control strategies focusing on reducing *T. vaginalis* may have a significant impact on reducing HIV transmission among both women and men.
- Transmission of trichomoniasis is higher from men to women and it may be detected in about 5% of newborn girls born to infected mothers.
- Trichomoniasis is asymptomatic in 50% of women and 90% of men.
- Definitive diagnosis of trichomoniasis requires demonstration of the organism. The vaginal pH is usually greater than 5, and a gray or yellow-green, malodorous discharge may be present.
- All patients with trichomoniasis and their recent sexual contacts require therapy, with metronidazole (Flagyl) being the drug of choice. Treatment with vaginal preparations may not result in complete eradication of the organism.
- For (rare) metronidazole-resistant trichomoniasis, the use of metronidazole, 1 to 2 g four times a day, for 10 to 14 days will us ually result in eradication of the organism.
- The most common causes of vulvovaginitis in the pediatric population are poor hygiene, threadworms, and foreign body.

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CHAPTER 5

Abnormal Cervical Cytology and Human Papillomavirus

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Although the incidence of female cervical neoplasia has plateaued in the developed world, it continues to remain a major cause of morbidity and mortality in the developing world. Nearly one-half million women are expected develop cervical cancer each year, and 80% of women will die each year from complications related to their cancer.[1,2] With the introduction of the Papanicolaou (Pap) smear (or test) and cytologic universal screening programs in the United States and other developed countries, mortality rates from cervical cancer have decreased by 46% from 1973 to 1995.[3] Cervical cancer currently represents nearly 1% of female cancer deaths, and although decreasing in incidence, remains a major health problem in the United States. An estimated 12,170 new cases of invasive cervical cancer are diagnosed in the United States in 2012, leading to nearly 4220 deaths in the United States alone.[4] In the developing world, the numbers are far greater. Worldwide cervical cancer remains the most common cancer affecting women resulting in over 275,000 deaths per year (You have free access to this content).[5]

The annual incidence of cervical intraepithelial neoplasia (CIN) for women in the United States who undergo cervical cancer screening is estimated to be 4% for CIN 1 and 5% for CIN 2 and 3.[6] The high-grade lesions (CIN 2 and 3 or high-grade squamous intraepithelial lesions [HSIL]) are usually found in women aged 25 to 35 years, whereas invasive cervical cancer is typically seen after the age of 40 years.

The financial burden of cervical cancer treatment on the American health care system is estimated to be over 2 billion dollars.[7] Sadly, racial and economic disparities exist with regards to the incidence of cervical carcinoma. Death from cervical cancer is twice as common among Hispanic women and four times as common in African American women compared to Caucasian women.[8,9]

Because cervical cancer is practically nonexistent in women who have never been sexually active, sexual activity is a dominant risk factor for CIN. The causal association between sexual activity and CIN and/or cervical cancer is infection with the human papillomavirus (HPV).[10] Recent studies have concluded that among women with normal cervical cytology, the estimated prevalence of HPV is as high as 10% worldwide.[11] When considering other behavioral, sexual, and socioeconomic factors, their relationship to CIN clearly depends on the presence of HPV infection and are not independent risk factors.[12]

There is emerging evidence that the oncogenicity of HPV infection may extend well beyond the female anogenital region. The potential role of HPV infection in the development of oropharyngeal, tonsillar, and lung cancer is currently under investigation.[13,14] As our understanding of the carcinogenesis of cervical cancer and its precursors continues to evolve, screening methods are being refined and guidelines revised in an attempt to decrease the incidence of this now preventable disease. This chapter provides an overview of the crucial role of HPV as the etiologic agent of cervical dysplasia and cancer; risk factors for progression, screening, and management of cervical precursor lesions; and preventative measures. The recognition and treatment of vaginal, vulvar, and anal intraepithelial neoplasia (AIN) are also discussed.

HUMAN PAPILLOMAVIRUS

Epidemiology

HPV infection of the male and female anogenital tract is the most common sexually transmitted disease in the United States. Infection with HPV is strongly associated with both cervical dysplasia and cervical cancer. In fact, 99.7% of cervical neoplasia is attributable to HPV infection.[15] HPV can infect almost all human skin and epithelial surfaces with potential oncogenicity in those sites, both in males and females. Viral transmission requires intimate contact between partners but does not depend on sexual penetration or intercourse for its transmission. Most HPV infections occur in young women and are transient. In a study in the United States, the prevalence of HPV among women aged 14 to 59 years was about 27%.[16] The same study found that approximately 25% of girls ages 14 to 19 years had detectable HPV infection at the time of the analysis. The percentage of detectable HPV infection for other age groups were as follows: 34% of women ages 20 to 24 years, 27% of women ages 25 to 29 years, 28% of women ages 30 to 39 years, 25% of women ages 40 to 49 years, and 20% of women ages 50 to 59 years.[16] In sexually active women, the point prevalence of HPV infection declines after 30 years of age, but there is an

increase in point prevalence after age 50 years that may be related to changes in immune and hormonal status that occur following menopause.[16–18] Important to also note is a change in lifestyle or sexual partners in women of any age, which may lead to new HPV infection.

Although HPV infection is a necessary element for the development of cervical neoplasia, it is transient in 90% of women and becomes undetectable in 2 years.[19] Risk factors for acquiring HPV include sexual behavior, increasing frequency of sexual intercourse, early age of first coitus, number of lifetime sex partners, the male partner's number of lifetime sex partners, age, ethnicity, HIV infection, and smoking or living with smokers.[12,17,20] Smoking is thought to potentiate the oncogenic potential of the HPV. Various carcinogens concentrate in cervical mucus and thus further contribute to oncogenesis.[21] Factors such as oral contraceptive use, increased gravidity, and immunosuppression have been reported but are less clearly associated. Most infections with HPV are transient or intermittent, with a median duration of 8 months.[17,18,22] Although adolescent women are at increased risk for infection due to the immature transitional zone (ectropion) of the cervix, both young and adolescent women are more likely to clear the infection. HPV infections and early cervical dysplasia represents a transient infection with up to 60 and 91% regression at 12 and 36 months, respectively, in women younger than 21 years of age.[23] Considerable geographic variation in the distribution of HPV genotype has been reported. Women in Europe appear to be more likely infected with HPV-16 than women in sub-Saharan Africa. Also, in Europe and the United States, the most common oncogenic HPV genotypes remain 16 and 18.[11,16,24]

It is clinically important to know that prior infection with any one or multiple types of HPV has not been shown to confer immunity or protection from acquisition of another type of HPV.[25] This is also true with the vaccines, which are widely underused and which will be discussed further.

Human Papillomavirus and Cervical Disease

HPV is linked to almost 100% of cervical cancer cases. HPV acquisition may result in several outcomes, including clearance of infection, active or persistent infection, progression to precancerous invasion, and even neoplastic transformation. Clearance of the infection is by far the most common sequelae, and there are no physical, cytologic, or histologic manifestations. In active infection, the HPV undergoes replication but is not integrated into the cellular genome. Active infection results in characteristic cytologic changes, for example, perinuclear halos and nuclear enlargement, which appear 2 to 8 months after initial infection.[26] The cytologic changes associated with active infection are the characteristics of atypical squamous cells of undetermined significance (ASCUS) and low-grade intraepithelial lesions (LSIL), and resolution of the infection is associated with regression of the cytologic changes as well. In instances of neoplastic transformation, the HPV genome becomes integrated into the cellular genome and may manifest as high-grade lesions or cancer years after the initial infection.

TABLE 5.1 High-Risk and Low-Risk Types of Human Papillomavirus

High-Risk Types	Low-Risk Types
16, 18, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 66, 68	6, 11, 26, 42, 44, 54, 70, 73

The oncogenic potential among the different types of HPV and the relative risk of oncogenicity for various HPV genotypes is displayed in Table 5.1. HPV infection with oncogenic potential (high risk) is associated with a four-fold increased risk of developing ASCUS and/or LSIL as well as a 13-fold risk of developing HSIL. The presence of high-risk HPV also substantially increases the time to regression and decreases the time to progression of cervical lesions.[27] Women with high-risk genotypes of HPV infection, especially HPV-16, have an even higher risk of developing HSIL than those with low-risk genotypes.[28] Rates of progression and/or persistence of high-grade dysplasia of ASCUS, LSIL, and HSIL are about 7, 21, and 24%, respectively, at 24 months among patients infected with high-risk genotypes. The progression trends of cervical dysplasia are displayed in Table 5.2. Ultimately, however, less than 1% of women infected with oncogenic HPV types develop invasive cervical cancer.[29] Therefore, current models of HPV-related carcinogenesis emphasize the role of persistent infection, immune factors, and cocarcinogens in the progression of asymptomatic infection to dysplasia and carcinoma (Fig. 5.1).[3,17,22,30]

Human Papillomavirus Testing

Epithelial cells have the strongest predilection for HPV infection. The anatomic sites that provide a favorable

TABLE 5.2 Natural History of Cervical Lesions

Biopsy Result	Regress	Persist	Progress to Carcinoma in Situ	Progress to Invasion
CIN 1	57%	<32%	11%	>1%
CIN 2	43%	<35%	22%	>5%
CIN 3	32%	<56%	—	>12%

CIN, cervical intraepithelial neoplasia.
Adapted from Östör AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol.* 1993;12:186–192; Melnikow J, Nuovo J, Willan AR, et al. Natural history of cervical squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol.* 1998;92:727–735.

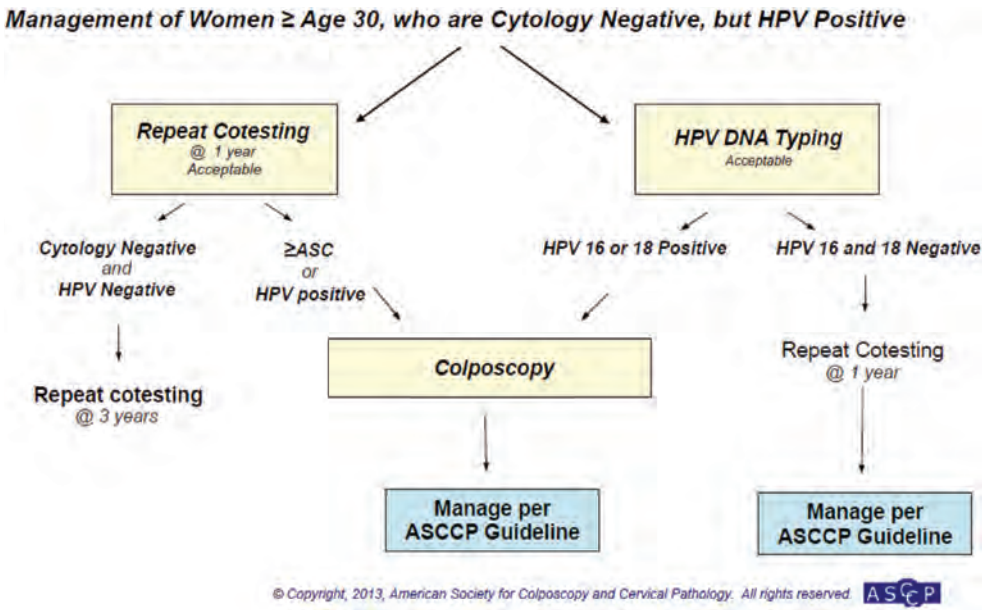

FIGURE 5.1 Management of women age 30 years and older who are cytology negative but HPV positive. (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

environment for viral infection are the cervix, vaginal, vulva, anus, and oropharyngeal mucosa surfaces. Attempts at culturing HPV from tissue samples or growing the virus in tissue culture have been unsuccessful thus far. In addition, the epithelium appears to shield the virus from the immune response, making serologic tests relatively unreliable.[31,32] At present, the diagnosis of HPV infection requires direct detection of viral DNA within the nucleus of an infected cell. Samples from the transformation zone (TZ) of the cervix collected by cytobrush are generally a good source of infected cells. The relationship between HPV infection and subsequent development of anogenital neoplasia is so compelling that the possibility of HPV-negative LSIL as a distinct biological entity is now shown to be unfounded. Most such findings appear to stem from cytologic misinterpretations or falsely negative HPV tests.[33]

Several assays for the detection of HPV have been developed, each with different sensitivities and specificities, depending on the method of DNA extraction from the cervical sample and the amount of DNA used. Most assays use direct hybridization techniques or nucleic acid amplification, such as the polymerase chain reaction (PCR). The two major assays currently being used to detect HPV in the United States use Hybrid Capture (HC) assay technology and include the HC II High-Risk HPV DNA test and DNA with Pap (both by Digene, Inc., Gaithersburg, MD). HC II can be performed on samples collected in the manufacturer's media or other commercially available liquid-based cytology systems (e.g., ThinPrep by Cytyc Corp., Boxborough, MA). In 2009, Hologic produced the first test able to specifically test for HPV-16 and -18 (Cervista HPV DNA HR Test). In 2011, cobas HPV DNA 4800 (Roche) and Aptima HPV mRNA HPV (Gen-Probe) tests were Food and Drug Administration (FDA) approved.[34]

SCREENING FOR CERVICAL CANCER PRECURSORS

Cervical dysplasia is highly treatable, making cervical cancer almost completely preventable. For example, only 1% of treated CIN 3 will become invasive. Left untreated, however, 30% of these same lesions will become cancer over a 30-year period.[35] It is estimated that 50% of women in the United States with newly diagnosed invasive cervical carcinoma have never had a Pap smear, and the other 50% occur in women who were poorly screened (e.g., had not had a Pap smear in the last 5 years), received inadequate follow-up, or were cases associated with technical errors of the Pap test process.[36] Similar results have been found in Europe.[37] The same could not be said in developing countries with varying technological and resource limitations. Nonetheless, attempts to improve both screening modalities and early detection of cervical cancer precursors, as well as timely intervention, remain major public health goals worldwide (Fig. 5.2).

The development of new screening and management guidelines is a useful adjunct to help clinicians avoid the pitfalls of under- or overtreatment (Table 5.3 and Figs. 5.1 through 5.10). Because guidelines will likely change in the future, up-to-date information is available at http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm and http://www.asccp.org. Additionally, mobile device applications are available.

Liquid-Based Cytology

Although long recognized as a highly effective screening test, the validity of the conventional Pap smear has been the center of controversy due to a significant false-negative rate related in part to errors in sampling and fixation

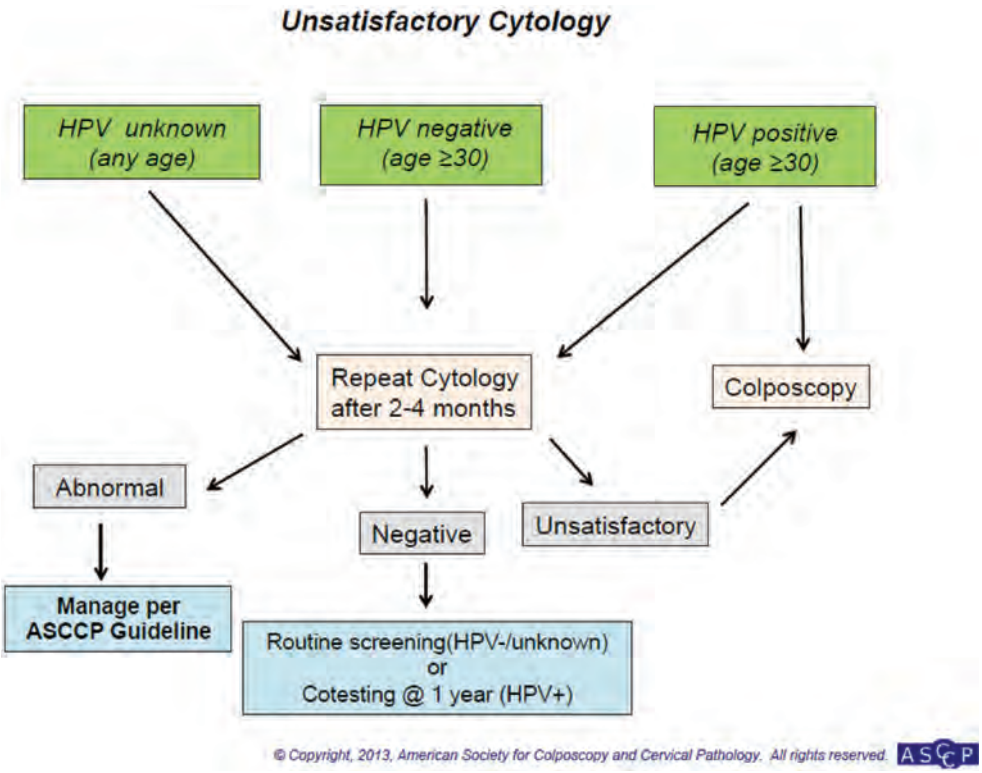

FIGURE 5.2 Unsatisfactory cytology. (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

as well as inaccurate and nonreplicable interpretation. Studies in the United Kingdom have shown a sensitivity rate of conventional Pap smears of 72% and specificity of 94%.[38] Overall, about two-thirds of the false-negative Pap tests were related to sampling errors and the remaining one-third due to laboratory detection error. Liquid-based screening systems were developed to improve the transfer of cells from the collection device to the slide, provide uniformity of the cell population in each sample, decrease obscuration of menstrual blood flow, and thus decrease interpretational errors. Studies have shown liquid-based cytology to be better at providing an adequate specimen and detecting ASCUS, LSIL, and glandular abnormalities. This method is not better at detecting the clinically relevant HSIL.[39–43]

Additionally, no systematic reviews have shown liquid-based cytology to be superior overall.[42,44]

Added benefits of liquid-based cytology systems include the ability to perform "reflex" HPV testing and detection of other concurrent infections (gonorrhea, chlamydia, etc.). Many health care providers have therefore made liquid-based cytology their test system of choice despite higher cost. The two systems currently available are ThinPrep and SurePath (TriPath Imaging, Inc., Burlington, NC).[45,46]

Human Papillomavirus Testing as a Screening Modality

HPV testing (referrers to high-risk genotypes) has two benefits: increasing disease detection and increasing screening intervals. Multiple studies have shown the increased sensitivity of HPV testing compared to Pap smears especially in the cases of CIN 3 or more and adenocarcinoma in situ (AIS).[47] The high sensitivity of HPV testing combined with a high negative predictive value means a negative test result should be very reassuring for patients and their health care providers. Patients younger than 21 years of age should not be screened by any modality regardless of sexual history. HPV testing as a primary screening modality in patients 21 to 29 years of age is not currently recommended because the rate of HPV infection is high in this age group. HPV testing would be more prudent as a triage modality in these patients. HPV "cotesting" (HPV with cytology) is recommended in women 30 to 65 years of age (see Table 5.3). HPV testing could also be an option in resource-poor areas because patient-collected specimens were similarly effective as Pap smears with colposcopy in a large African study.[48]

Human Papillomavirus Testing as a Triage Modality

For many years, a plethora of evidence has shown HPV is associated with almost 100% of high-grade dysplasia and cervical cancer. This lead to investigations, such as the ALTS (ASCUS LSIL Triage Study) trial, demonstrating that patients who are HPV negative could be managed conservatively.[49] Additional research further categorized HPV into the low- and high-risk genotypes, refining our ability to triage even more. Most recently, studies have shown that HPV type 16 (HPV-16) causes 55 to 60% of cervical

TABLE 5.3 Summary of Recommendations

Population	Page Number	Recommended Screening Method[a]	Management of Screen Results	Comments
Age <21 years	7	No screening		HPV testing should NOT be used for screening or management of ASCUS in this age group.
Age 21–29 years	8–9	Cytology alone every 3 years	HPV-positive ASCUS[b] or cytology of LSIL or more severe: Refer to ASCCP Guidelines[c] Cytology negative or HPV-negative ASCUS[b]: Rescreen with cytology in 3 years	HPV testing should not be used for screening in this age group.
Age 30–65 years	9–16	HPV and cytology "cotesting" every 5 years (preferred)	HPV-positive ASCUS or cytology of LSIL or more severe: Refer to ASCCP Guidelines[c] HPV positive, cytology negative: Option 1—12-month follow-up with cotesting Option 2—test for HPV-16 or HPV-16/18 genotypes If HPV-16 or HPV-16/18 positive: refer to colposcopy If HPV-16 or HPV-16/18 negative: 12-month follow-up with cotesting Cotest negative or HPV-negative ASCUS: Rescreen with cotesting in 5 years	Screening by HPV testing *alone* is not recommended for most clinical settings.
		Cytology alone every 3 years (acceptable)	HPV-positive ASCUS[b] or cytology of LSIL or more severe: Refer to ASCCP Guidelines[c] Cytology negative or HPV-negative ASCUS[b]: Rescreen with cytology in 3 years	
Age >65 years	16–17	No screening following adequate negative prior screening		Women with a history of CIN 2 or a more severe diagnosis should continue routine screening for at least 20 years.
After hysterectomy	17–18	No screening		Applies to women *without* a cervix and *without* a history of CIN 2 or a more severe diagnosis in the past 20 years or cervical cancer ever.
HPV vaccinated	18–19	Follow age-specific recommendations (same as unvaccinated women)		

HPV, human papillomavirus; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade intraepithelial lesions; ASCCP, American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia.
[a]Women should not be screened annually at any age by any method.
[b]ASCUS cytology with secondary HPV testing for management decisions.
[c]From Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012;62:147–172; Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Lower Genital Tract Dis.* 2013;17(5):S1–S27.

cancer. HPV-18 causes 10 to 15% of cervical cancers, including a greater proportion of glandular cancers. These subtypes can be specifically tested for on the cobas HPV test or Cervista 16/18 test. The remaining 25 to 35% of cervical cancer is caused by 13 other genotypes.[50–52]

Therefore, HPV reflex testing is especially useful for ASCUS, allowing referral to colposcopy for HPV-positive patients and surveillance for those without. The management of patients with ASCUS Pap smears has been particularly problematic because adherence with the recommended follow-up smear in 6 months tends to be poor, and many patients are lost to follow-up. This is concerning because studies have shown that patients with a diagnosis of ASCUS have a 5 to 17% chance of harboring high-grade dysplasia.[53] Conversely, harm can be done (psychological, financial, physical) by further management and treatment of lesions that were destined to resolve. The ability to triage is invaluable for this cytology. HPV testing can also be used for management of women with LSIL.[54] Furthermore, a patient with normal cytology and a positive HPV test can be further investigated for types 16 and 18 to determine her need for immediate colposcopy versus repeat cotesting in 1 year.[55]

Initiation of Screening and Screening Intervals

In 2009, the American College of Obstetrics and Gynecologists (ACOG) and the American Cancer Society

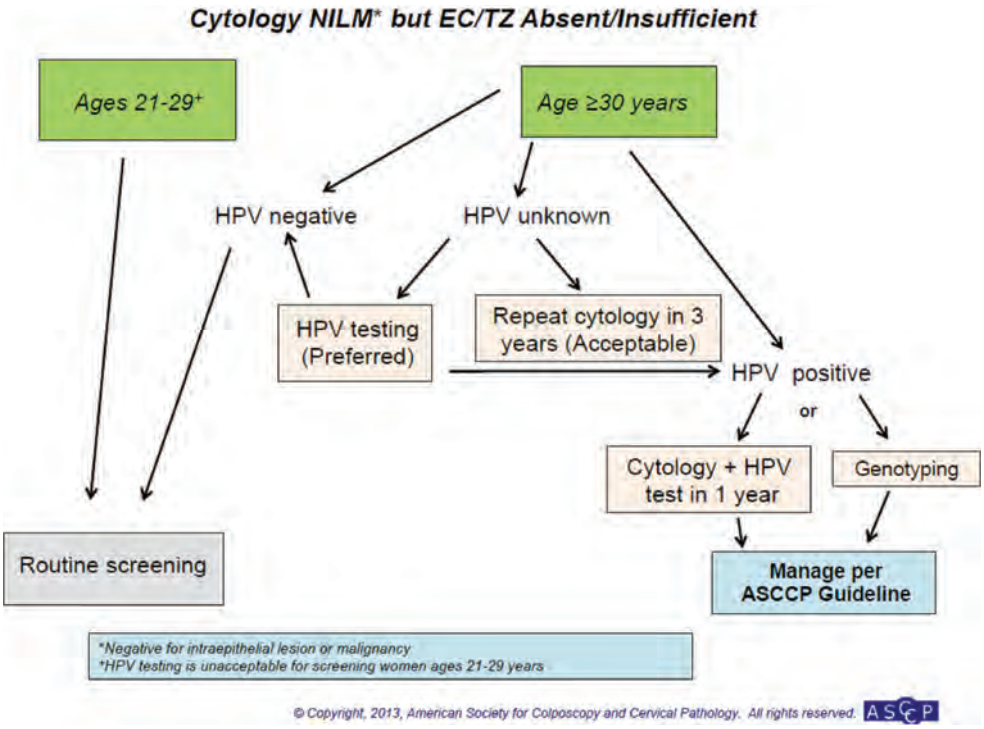

FIGURE 5.3 Cytology NILM* but EC/TZ Absent/Insufficient. (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

(ACS) amended its previous recommendations for screening women for cervical cancer. This was further revised in 2012 (see Table 5.3).[56] The first major change involves initiation of screening. Previous guidelines recommended that women begin screening at age 21 years or 3 years after age at first coitus and that screening be continued annually until age 30 years. The current recommendations now instruct practitioners to *begin screening at age 21 years and screen every 3 years* thereafter until age 30 years. Initiation of screening is *independent of age of first coitus* and should only commence at age 21 years. In the case that an adolescent presents with known ASCUS or LSIL, cytology should be repeated in 1 year. Those that present with HSIL should

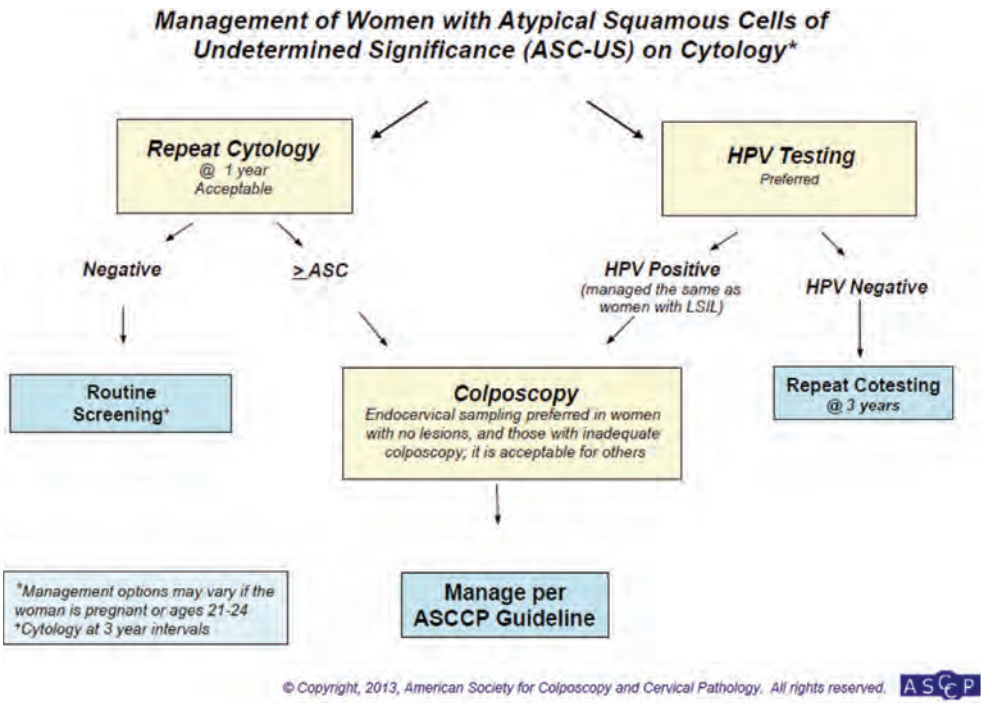

FIGURE 5.4 Management of women with atypical squamous cells of undetermined significance (ASCUS) on cytology. (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

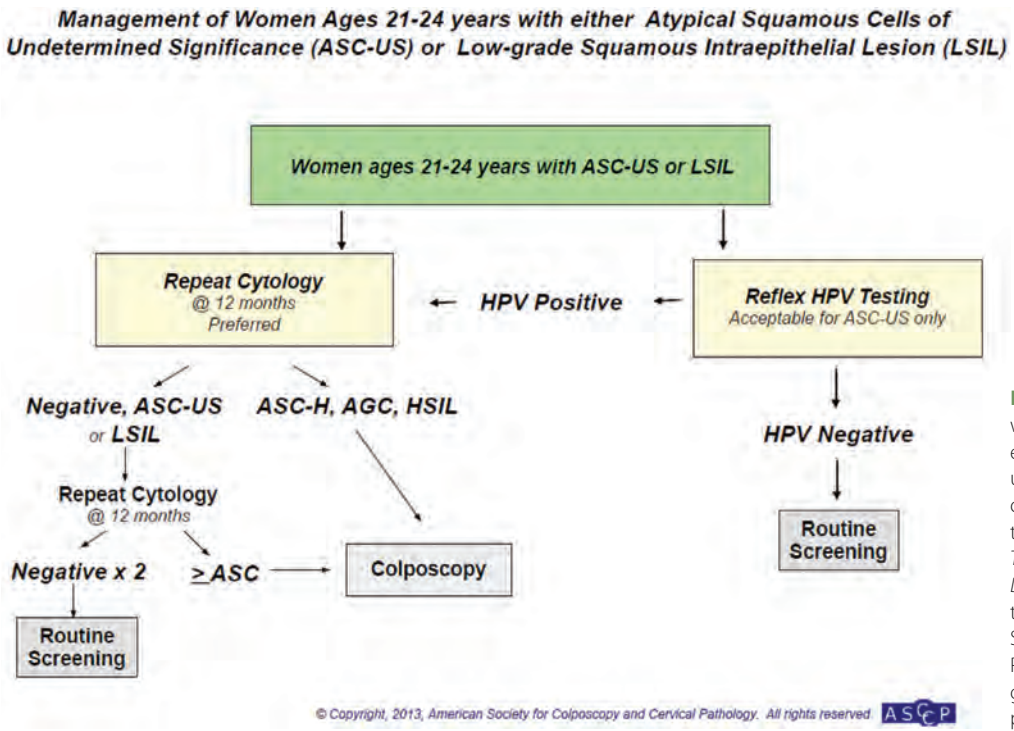

FIGURE 5.5 Management of women ages 21 to 24 years with either atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

go to colposcopy. The evidence behind changing screening initiation age and interval is two-fold. First, given the prevalence of initial HPV infection in adolescents and those younger than 21 years, many young women will transiently be infected with HPV. Most of these women will clear the infection and not go on to develop cervical dysplasia. Screening before 21 years of age would therefore increase the number of surgical interventions for transient disease with virtually no risk for the development of invasive cervical cancer. Secondly, yearly screening between the ages of 21 and 30 years has not been shown to decrease the incidence of cervical cancer given the 5 to 10 years needed to develop disease.

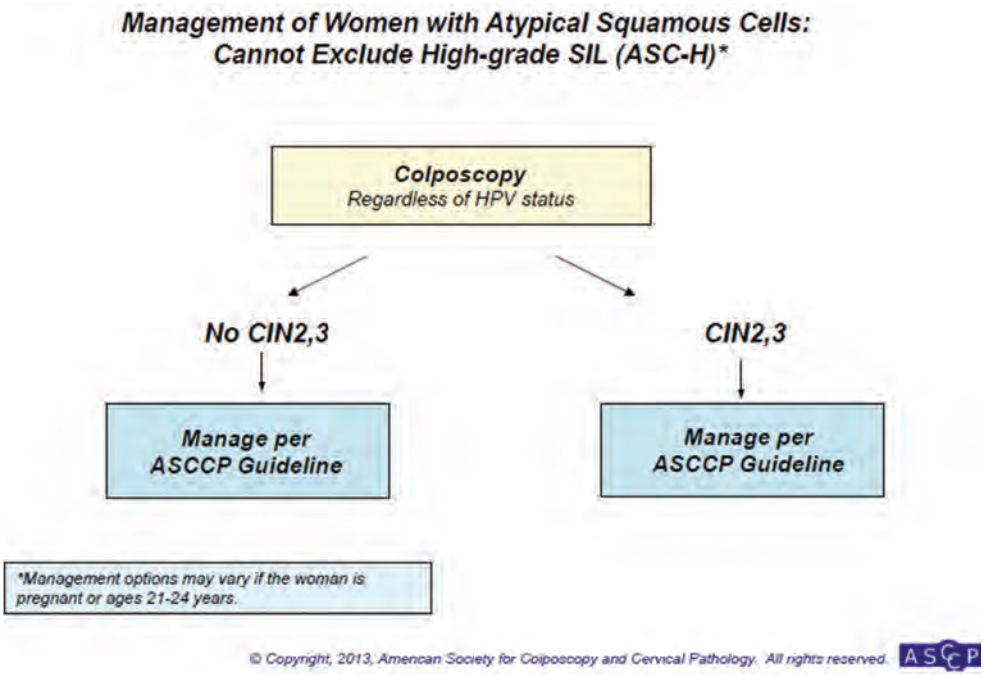

FIGURE 5.6 Management of women with atypical squamous cells: cannot exclude high-grade SIL (ASC-H). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

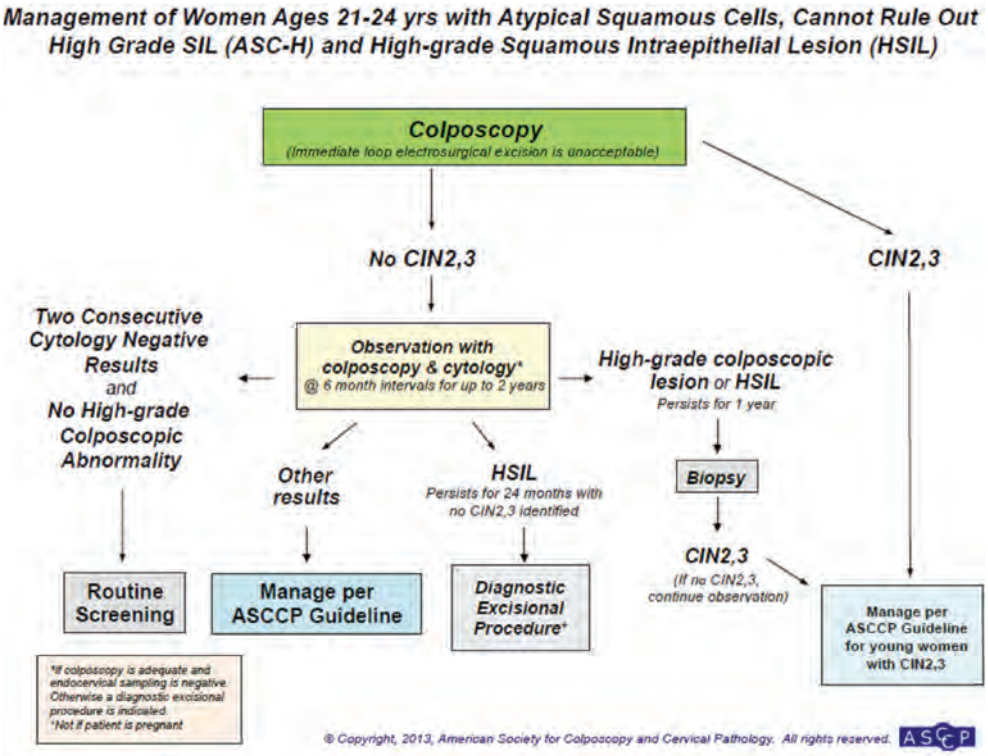

FIGURE 5.7 Management of women ages 21 to 24 years with atypical squamous cells: cannot rule out high-grade SIL (ASC-H) and high-grade squamous intraepithelial lesion (HSIL). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

The second major change to screening guidelines involves cotesting. Women younger than the age of 30 years should not be screened with HPV because the prevalence and resolution of infection is high in this group. The preferred screening for women 30 to 65 years of age is via cotesting. If negative, they can be screened every 5 years because the risk for CIN 3 or adenocarcinoma is low.

A third change is management of HPV-positive, cytology-negative Pap smears in women age 30 years and older. There are two options. The practitioner can (a) repeat cotesting in 12 months or (b) order HPV genotype-

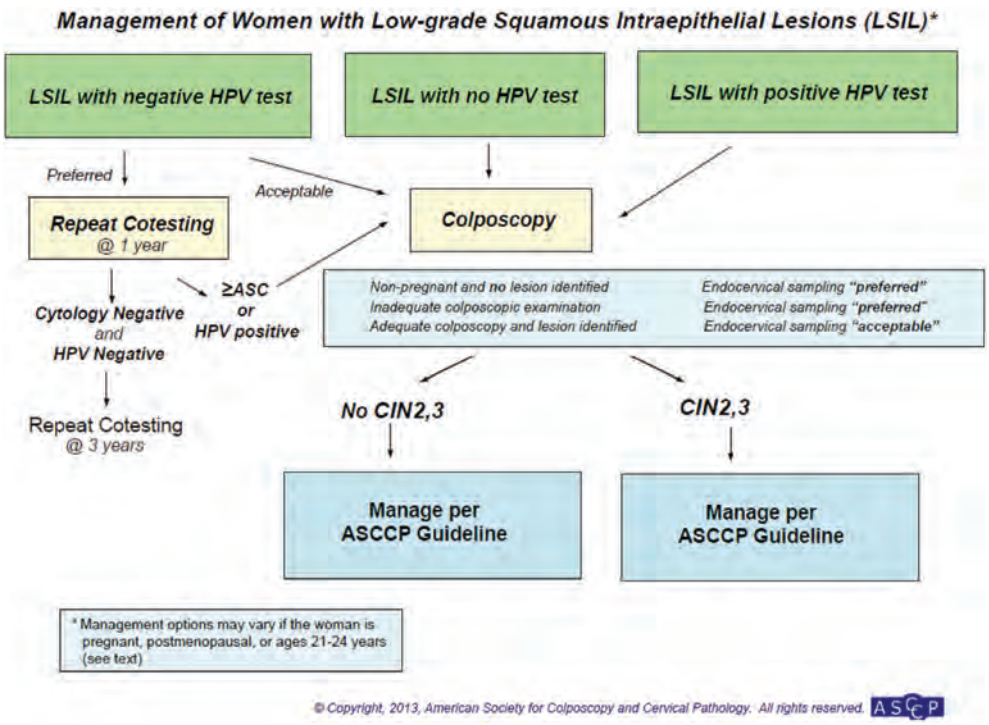

FIGURE 5.8 Management of women with low-grade squamous intraepithelial lesions (LSIL). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

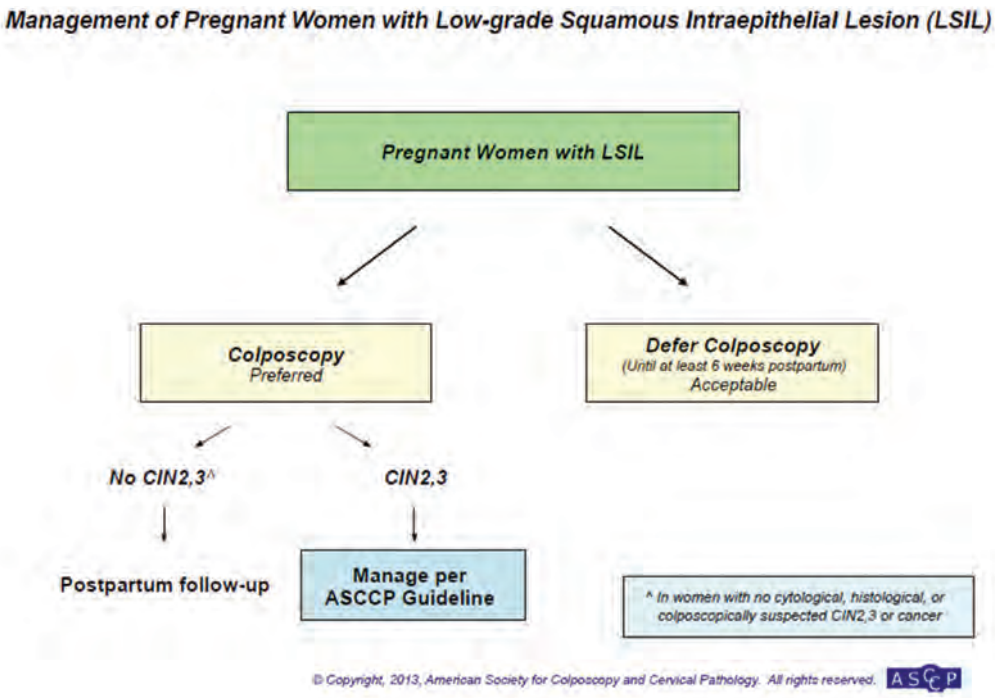

FIGURE 5.9 Management of pregnant women with low-grade squamous intraepithelial lesion (LSIL). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

specific testing for 16/18. If HPV-16/18 are present, the patient should be immediately referred for colposcopy. If they are HPV-16/18–negative, they can be followed up in 12 months with cotesting (see Fig. 5.3).

The final change is the addition of the 21- to 24-year age group as a subcategory, and which includes more conservative management recommendations than those for women age 25 years and older.

MANAGEMENT OF CERVICAL DYSPLASIA

Consensus guidelines for the screening and management of abnormal cervical cytology underwent review in 2006 and again in 2009 where specific changes in guidelines for the initiation of screening and management of abnormal Pap smears in adolescents, pregnant women, postmenopausal women, and those with HIV were

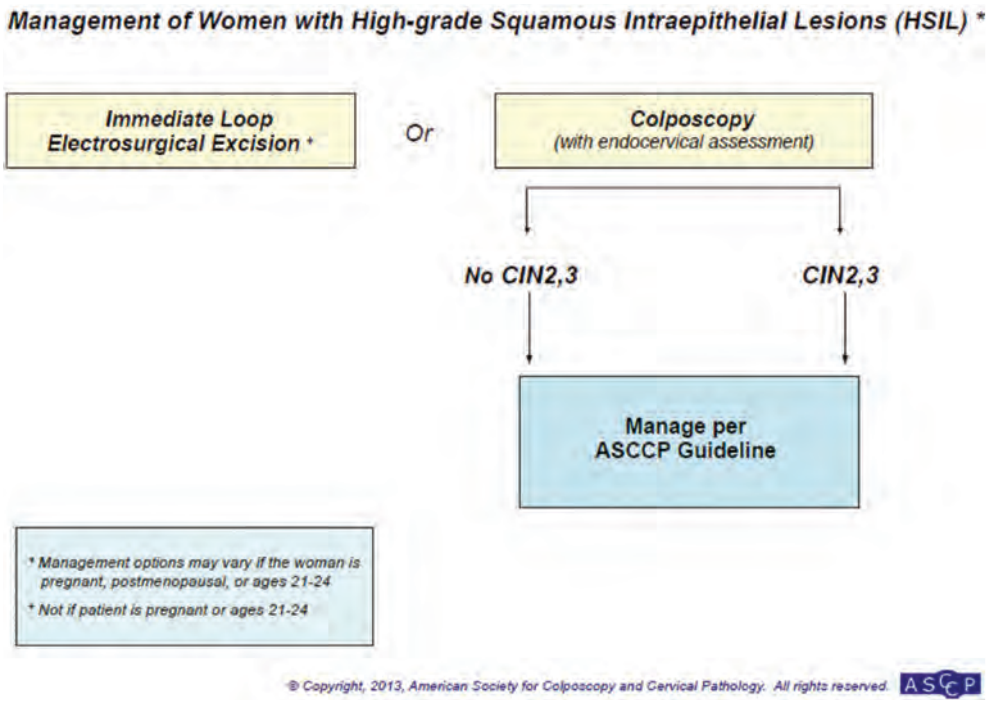

FIGURE 5.10 Management of women with high-grade squamous intraepithelial lesions (HSIL). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

made.[57] Another review was made in September 2012 with new American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines published in 2013 for the management of patients with unsatisfactory cytology, absent/insufficient endocervical cells, or negative cytology with HPV (see Figs. 5.1 through 5.3).

Management of Women With Atypical Squamous Cells of Undetermined Significance

A diagnosis of ASCUS or ASC no longer represents a management challenge for practitioners. One can either get reflex HPV testing (preferred) or repeat the cytology at 12 months. If she is HPV negative, the patient returns for cotesting in 3 years. If positive, she is referred to colposcopy; Figure 5.4 illustrates the management algorithm for women with ASCUS. The disadvantages of repeat cytology even in adherent patients are obvious because a delay in diagnosis and treatment of dysplasia is inevitable, and the false-negative rate of repeat cytology is high. Immediate colposcopy is no longer a recommended management option.

Atypical Squamous Cells of Uncertain Significance in Special Circumstances

The most common special circumstances include adolescent or young women, immunosuppressed women, pregnant women, and women with infection or reactive changes. Adolescents should not be screened. If screened, however, and it returns ASCUS, repeat cytology is recommended in 1 year. If repeat cytology shows HSIL, colposcopy is reasonable. If not, repeat cytology in 1 year is again recommended. If ASCUS persists (or the dysplasia progresses) for 24 months, colposcopy is recommended (see Fig. 5.5).[58]

All immunosuppressed women, even those with HIV, are managed the same as those in the general population. The management of pregnant women with ASCUS on Pap smear should be the same as in nonpregnant women except that endocervical curettage (ECC) is *not* performed. ECC in pregnancy is unacceptable. Infection found at the time of Pap smear should not be considered as the etiology for ASCUS. The patient should be treated if symptomatic or if she has a sexually transmitted infection. Postmenopausal women are no longer managed differently than premenopausal women.[59]

Management of Women With Atypical Squamous Cells—Cannot Exclude High-Grade Lesions

In general, any high-grade lesion warrants colposcopy and ECC. All patients with atypical squamous cells, cannot exclude high-grade lesions (ASC-H) should be referred for immediate colposcopy with ECC (except in pregnancy) as illustrated in Figures 5.6 and 5.7. For young women ages 21 to 24 years, immediate excision procedure is unacceptable (see Fig. 5.7). A subsequent finding of CIN 2 or CIN 3 lesions necessitates follow-up as outlined by ASCCP guidelines. If no CIN 2 or 3 lesions are found on biopsy, then cytology should be repeated at 6- and 12-month intervals or cytology with HPV DNA testing performed in 12 months. If at that time both cytology and HPV DNA tests are negative, the patient may revert to routine screening. If the patient, however, has ASCUS cytology or is now HPV positive, then colposcopy should be performed again.

MANAGEMENT OF SQUAMOUS INTRAEPITHELIAL LESIONS

The Bethesda System retains the two-tiered terminology of LSIL/HSIL. This distinction has been shown to be reproducible between pathologists, whereas the subdivision of cytologic HSIL into moderate and severe is more difficult to reproduce and is not included in the new Bethesda System. Hence, the three-tiered CIN 1/2/3 system may be used as an alternative to the LSIL/HSIL terminology or as an additional set of descriptive terms.

Management of Women With Low-Grade Squamous Intraepithelial Lesions

Nearly 15 to 30% of women with LSIL on Pap smear will have CIN 1, 2, or 3 on colposcopically directed biopsy.[60,61] The natural history of LSIL has been examined, and in one study of 151 patients, 34% of patients regressed, 55% had persistence, and 11% had progression to more concerning forms of dysplasia.[62] Furthermore, the vast majority of lesions are associated with HPV, so reflex testing is not cost-effective. However, if the patient had cotesting and the HPV was negative, she can have *repeat cotesting in 1 year*. The ASCCP recommends that all other women with LSIL undergo colposcopy (see Fig. 5.8) except for those in "special circumstances" (see the following discussion). Colposcopic findings of CIN 1 then require repeat cytology at 6 and 12 months or repeat HPV testing at 12 months. If negative, the patient can then proceed to routine screening. If repeat Pap is ASCUS or greater or HPV positive, a repeat colposcopy should be performed. CIN 2 and 3 on initial colposcopy should be managed per ASCCP guidelines.

Initial management of LSIL does not include any excision or ablative procedures because these are reserved for documented dysplasia. If colposcopy is satisfactory and a lesion is identified, a biopsy of the lesion should be performed with optional ECC. If no lesion is identified on colposcopy or in cases of unsatisfactory colposcopy (i.e., if a lesion is not seen in its entirety or if the TZ is not entirely visible), ECC should be performed, unless the patient is pregnant.

In situations of both satisfactory and unsatisfactory colposcopic examinations, where ECC and biopsy fail to detect dysplasia, several management options are available. Reassurance of the patient and HPV testing can be offered at 12 months with referral to colposcopy if positive for a high-risk type at that time. Alternatively, she can follow-up for repeat cytology in 6 and 12 months with referral for repeat colposcopy for a Pap smear of at least ASCUS. The risk of missing dysplasia in cases with satisfactory or unsatisfactory colposcopy with unidentifiable lesion is unclear.

Low-Grade Squamous Intraepithelial Lesions in Special Circumstances

Women ages 21 to 24 years should be followed in 12 months with repeat cytology, and only HSIL or greater is referred to colposcopy (see Fig. 5.5). If she has any dysplasia at 24 months, colposcopy should be performed. HPV testing should not be performed, and if it is, it should not influence management.

Postmenopausal women with LSIL Pap smears may be managed with reflex HPV testing or by repeating cytology in 6 and 12 months. If two negative repeat Pap smears are obtained, the patient may return to routine screening. If any repeat Pap smear is ASCUS or above, the patient should be referred to colposcopy.

Pregnant women with LSIL Pap smear can undergo colposcopy by an experienced clinician (preferred) or can be deferred until postpartum. Biopsy of lesions can be performed if high-grade dysplasia or cancer is suspected. Repeat examinations and ECC should not be performed on a pregnant patient. Similarly, diagnostic excision procedures are only indicated if invasive cancer is suspected. Excision procedures are associated with significant bleeding during pregnancy due to increased blood flow to the cervix and are therefore avoided unless the suspicion for invasive cancer is high. Follow-up colposcopy and cytology should be performed no sooner than 6 weeks postpartum (see Fig. 5.9).

Management of Women With High-Grade Squamous Intraepithelial Lesions

HSIL significantly increases a woman's chance of having advanced dysplasia (CIN 2 to 3) with studies estimating the risk as high as 70 to 75%.[63] HSIL confers a risk of progression of 2% for invasive cancer and up to 20% if precursor lesions are not treated or followed up.[64] In most cases, colposcopy should be immediately initiated and should be performed with endocervical assessment (see Fig. 5.10). Three possible scenarios emerge from colposcopic examination (Fig. 5.11). If the colposcopy findings suggest no CIN 2 or 3 lesions and the colposcopy is deemed unsatisfactory, a diagnostic excision procedure is indicated except in pregnant or young women (Fig. 5.12). By contrast, if the colposcopy is satisfactory and no CIN 2 or 3 lesions were found, the pathology should be reviewed and colposcopy with cytology should be initiated at 6-month intervals for 1 year. If repeat colposcopy and cytology at 6-month intervals demonstrate HSIL, the patient should undergo diagnostic excision procedure. If the patient has negative cytology status, routine screening should suffice. Lastly, if the biopsy confirms CIN 2 or 3, treatment is indicated (Fig. 5.13).

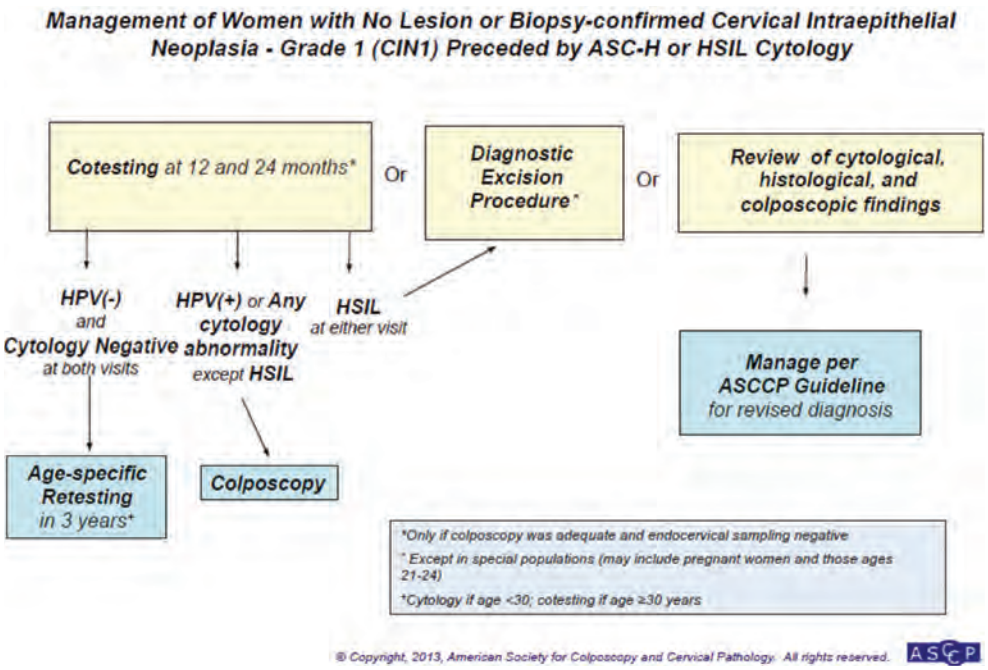

FIGURE 5.11 Management of women with no lesion or biopsy-confirmed cervical intraepithelial neoplasia—grade 1 (CIN1) preceded by ASC-H or HSIL cytology. (Reprinted from The *Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

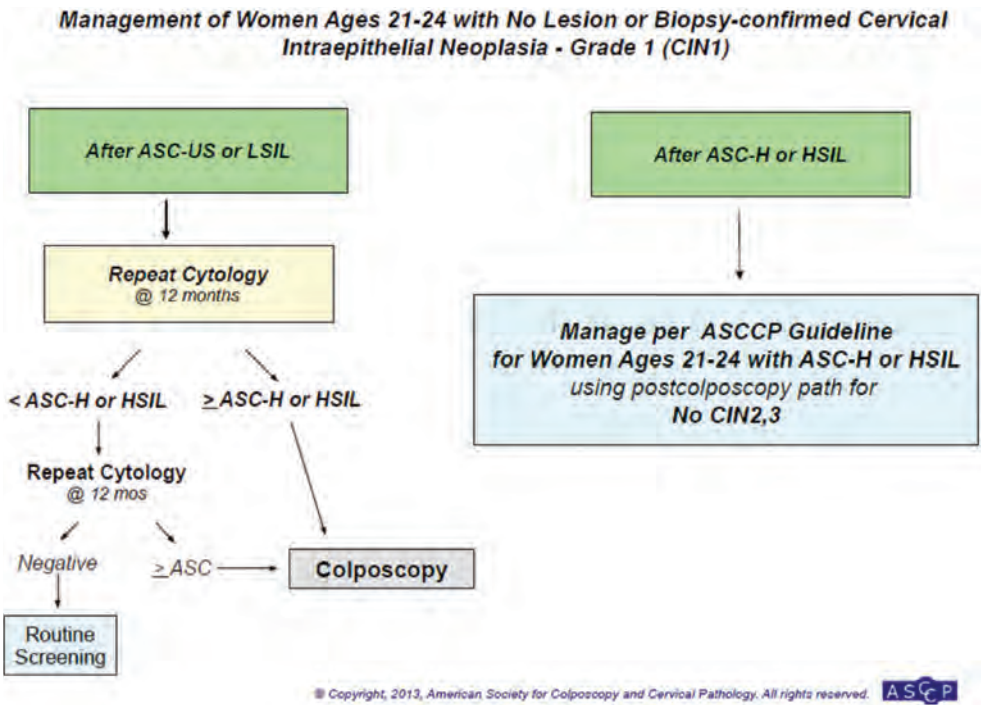

FIGURE 5.12 Management of women ages 21 to 24 with no lesion or biopsy-confirmed cervical intraepithelial neoplasia—grade 1 (CIN1). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

For young women, an immediate excision procedure is unacceptable. Some practitioners question whether a cervical lesion in a pregnant patient with HSIL on Pap should necessarily be biopsied because of concerns of increased bleeding risk. No reports of life-threatening hemorrhage or pregnancy loss secondary to cervical biopsies have been reported, but reserve biopsies for highly suspicious lesions. Excision procedures are reserved for suspicion of invasive cancer. As stated earlier, ECC is, however, contraindicated in pregnancy.

Among high-risk populations with large numbers of patients lost to follow-up, the so-called see and treat strategy has been advocated as a safe and cost-effective approach to treating women with HSIL, especially in the hands of an expert colposcopist.[65,66] This strategy allows for a loop electrosurgical excision procedure

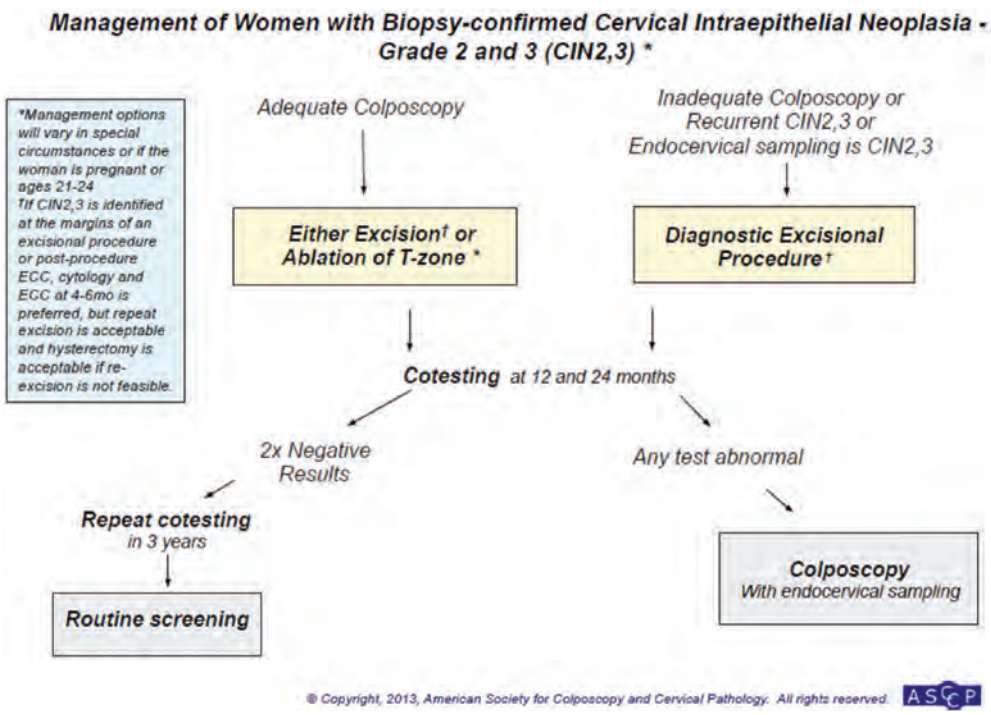

FIGURE 5.13 Management of women with biopsy-confirmed cervical intraepithelial neoplasia—grade 2 and 3 (CIN2,3). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume, 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

(LEEP) cone to be performed at the time of colposcopy if a suspicious lesion is identified. This should be reserved for women that have completed childbearing because a LEEP can double the risk of subsequent preterm delivery, a low-birth-weight infant, or premature rupture of membranes.[67,68] Young, nulliparous women with HSIL on Pap in whom no lesion with CIN 2 to 3 can be identified on colposcopy may be observed with repeat colposcopy and cytology every 6 months for up to 1 year because many lesions will regress.[69,70] If HSIL persists, a diagnostic excision procedure is indicated.

A high-risk HPV result of type 16 or 18 during cotesting may also help the practitioner decide to treat because these types, especially 16, have a high rate of progression to cancer.[71]

MANAGEMENT OF WOMEN WITH ATYPICAL GLANDULAR CELLS

A diagnosis of atypical glandular cells (AGC) is generally uncommon, with a reported frequency between 0.13 and 2.5%.[72,73] The overriding concern in patients with AGC Pap smears is the development of occult adenocarcinoma of the cervix. These cancers tend to have a more insidious course as compared to squamous cancers, and malignancy develops deep within the endocervical canal. A larger percentage (10 to 39%) of patients with AGC than those with ASCUS have been shown to have underlying high-grade lesions, including CIN 2, CIN 3, AIS, or invasive cancer.[74,75] Based on the initial Pap smear, the AGC are divided into atypical glandular cells not otherwise specified (AGC-NOS) or AGC favor neoplasia and a third category of endocervical AIS. Women with all subcategories of AGC and AIS should undergo colposcopy with ECC with HPV testing. In women older than age 35 years or other risk factors for endometrial lesions, endometrial sampling is also recommended. Colposcopy can be performed initially or after the results of the endometrial and endocervical biopsies are known (Fig. 5.14).

The management of patients with AGC is illustrated in Figure 5.15. The most common changes that result in an AGC Pap result include chronic cervicitis, endometriosis, and Arias-Stella reaction. The subsequent management plan depends on the initial Pap smear finding. If the initial Pap smear shows AGC (favor neoplasia) or AIS but no invasive disease on colposcopy, a diagnostic excision procedure of the cervix should be performed. This is due to a significant discrepancy between the cytologic and histologic findings. If the initial Pap smear on the other hand shows AGC-NOS, two possibilities exist. In one, the patient may have CIN but no glandular neoplasia or glandular neoplasia irrespective of CIN. In both cases, management should follow ASCCP guidelines for CIN. The second possibility is that there is neither CIN present nor glandular neoplasia. Cotesting at 12 and 24 months is then recommended. If both tests are negative, the patient should be reverted to routine screening, and if the tests demonstrate ASC or greater or HPV positivity, the patient should undergo colposcopy.

Benign-appearing glandular cells on a Pap smear in women older than age 40 years is a common finding and

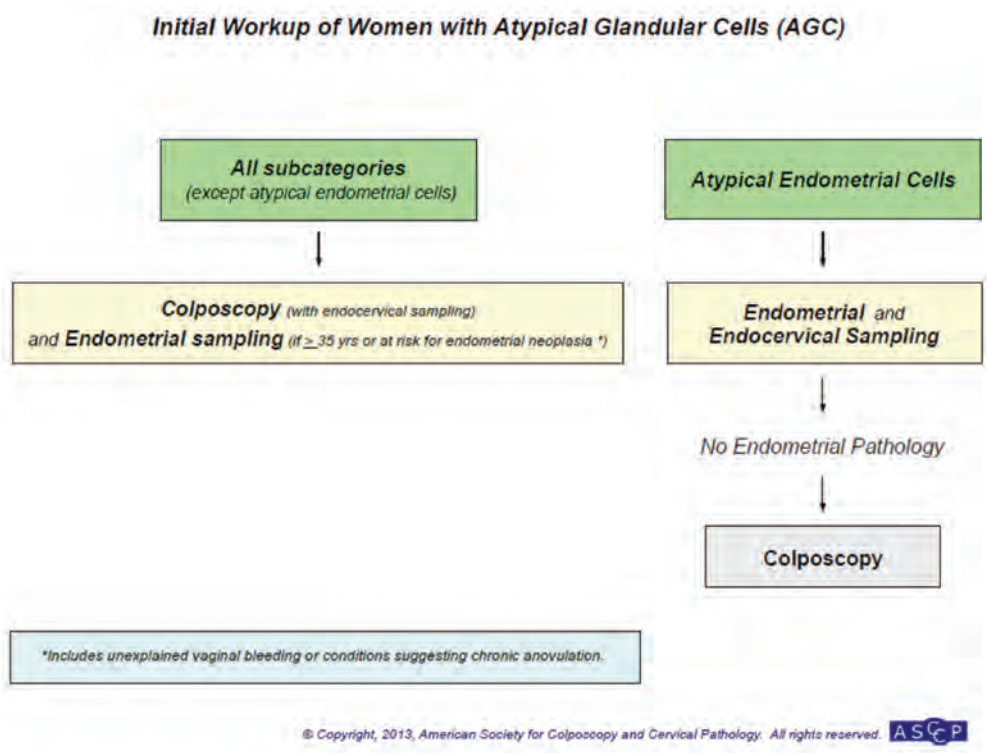

FIGURE 5.14 Initial workup of women with atypical glandular cells (AGC). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

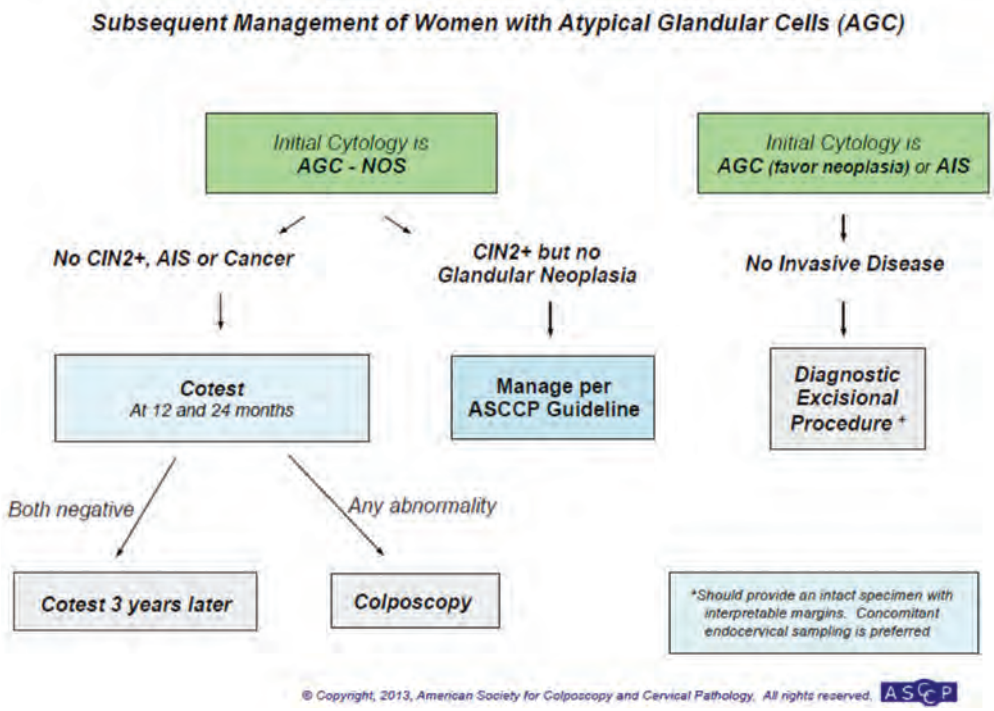

FIGURE 5.15 Subsequent management of women with atypical glandular cells (AGC). (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

is rarely associated with pathology. The corollary is true for postmenopausal women, so this necessitates an endometrial biopsy to screen for pathology.

MANAGEMENT OF CERVICAL INTRAEPITHELIA NEOPLASIA

Cervical Intraepithelial Neoplasia 1

Women with ASCUS or LSIL cytology can follow up without treatment. They should be cotested in 12 months and return to age-appropriate screening if HPV negative (Fig. 5.16). (Young women should have cytology only.) If the cytology was ASCH or HSIL, the patient may undergo repeat cotesting at 12 and 24 months or a diagnostic excision procedure (unless pregnant or younger than age 25 years) if the colposcopy was satisfactory and the ECC negative (see Figs. 5.11 and 5.12).

If the colposcopy is unsatisfactory and the ECC is negative, repeat cytology at 6 and 12 months can be performed. If the ECC is positive and the patient is finished with childbearing, an excision procedure should be performed. If she has not finished childbearing and is compliant, she could be followed or consideration should be given to a "shallow" LEEP with repeat ECC.

Although the risk of regression is still high for women with HIV, the risk of recurrence is more frequent. Use of antiretroviral therapy and other factors will play a role in this. For HIV-infected women with well-controlled disease, the same follow-up protocols could be used as in noninfected women. Otherwise, one could consider every 3 months follow-up with cytology, colposcopy with a low threshold for biopsy. Hysterectomy is an option for persistent CIN if childbearing is completed.

Cervical Intraepithelial Neoplasia 2 and 3

Treatment is recommended for both CIN 2 and 3 because the risk of progression is high (except in young and pregnant women) (see Fig. 5.13). Young women can be followed by repeat cytology and colposcopy at 6-month intervals for a year as long as the colposcopy is satisfactory, the ECC is negative, and the patient acknowledges the possibility of occult disease. In young women where CIN 3 is specified, treatment is preferred. Pregnant women can be followed each trimester with repeat colposcopy alone and then repeat cytology and colposcopy 6 weeks postpartum (PP) (Fig. 5.17).[76]

Adenocarcinoma in Situ

For AIS, hysterectomy is the preferred treatment, but it can be managed conservatively in patients desiring fertility. This requires negative margins and a negative ECC (Fig. 5.18).

DIAGNOSIS, TREATMENT, AND PREVENTION OF CERVICAL DYSPLASIA

Colposcopy

Colposcopy is a commonly performed procedure in the diagnosis of cervical dysplasia. Colposcopy is the close visual inspection of the cervix, vagina, and anogenital area using magnified illumination and the application

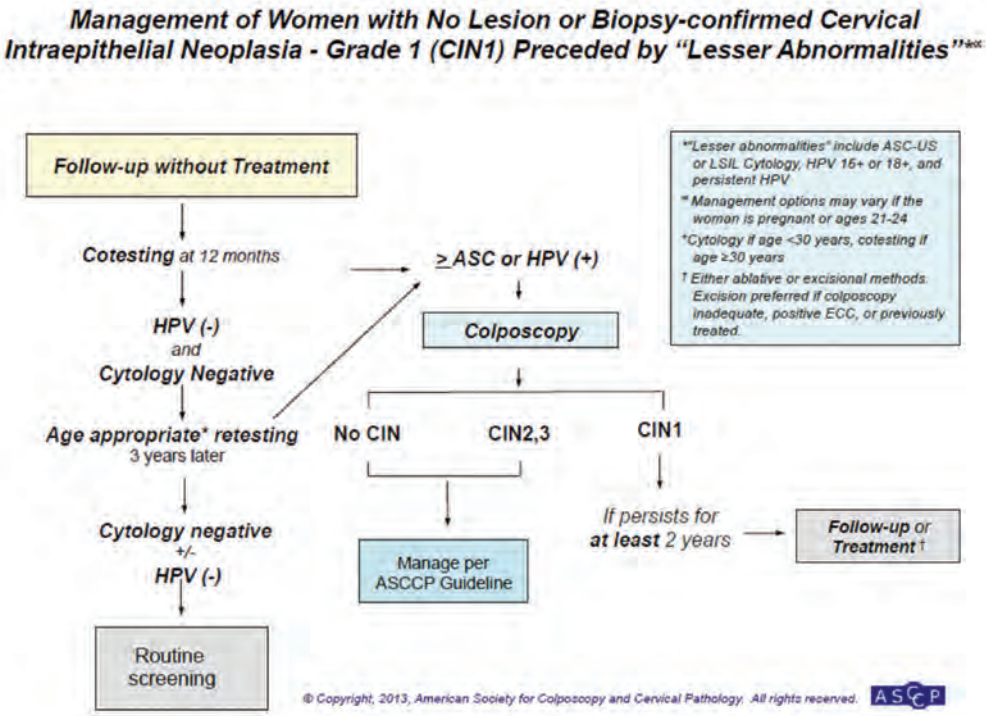

FIGURE 5.16 Management of women with no lesion or biopsy-confirmed cervical intraepithelial neoplasia—grade 1 (CIN1) preceded by "lesser abnormalities." (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

of specific solutions that highlight abnormal areas. Its main purpose is to help the clinician identify and biopsy target lesions and to rule out neoplasia. Colposcopy is indicated for any cytologic test showing ASCUS with a positive HPV test (except adolescents) or persistent ASCUS, ASC-H, AGC, LSIL, HSIL, or suspicion for invasive disease. A gross lesion on the cervix should be examined and biopsied colposcopically. Other indications for colposcopy usually include persistent high-risk HPV testing with normal cytology, postcoital or unexplained bleeding, history of exposure to diethylstilbestrol (DES) in utero, history of vulvar or vaginal neoplasia, or genital warts (condylomata acuminata).

A complete medical, surgical, and social history to elicit possible risk factors for cervical dysplasia should be obtained in all patients presenting for colposcopy

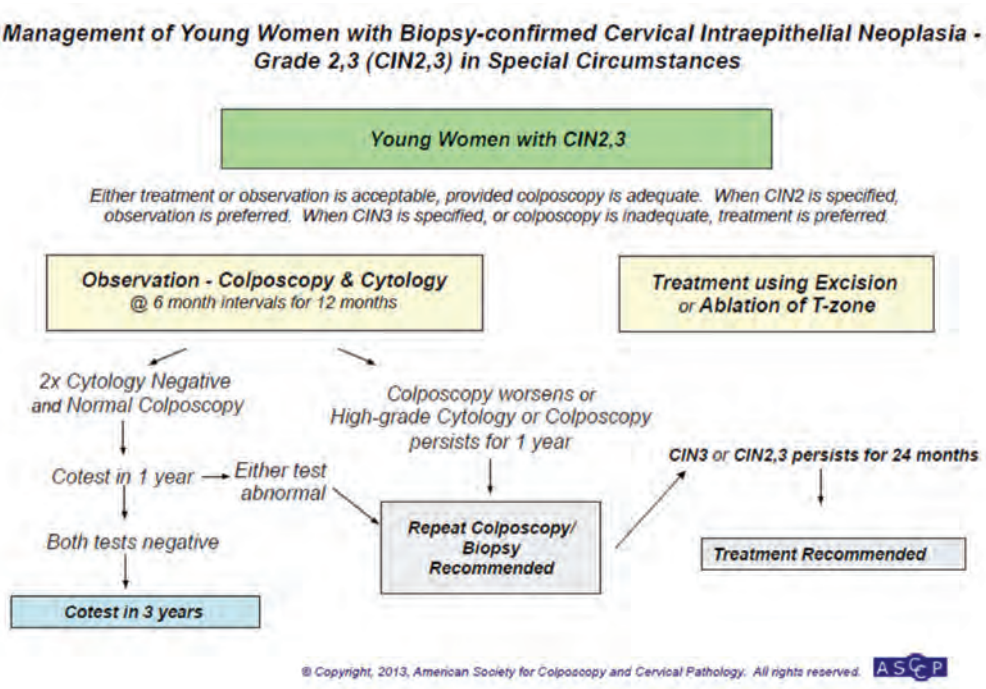

FIGURE 5.17 Management of young women with biopsy-confirmed cervical intraepithelial neoplasia—grade 2 and 3 (CIN 2 and 3) in special circumstances. (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

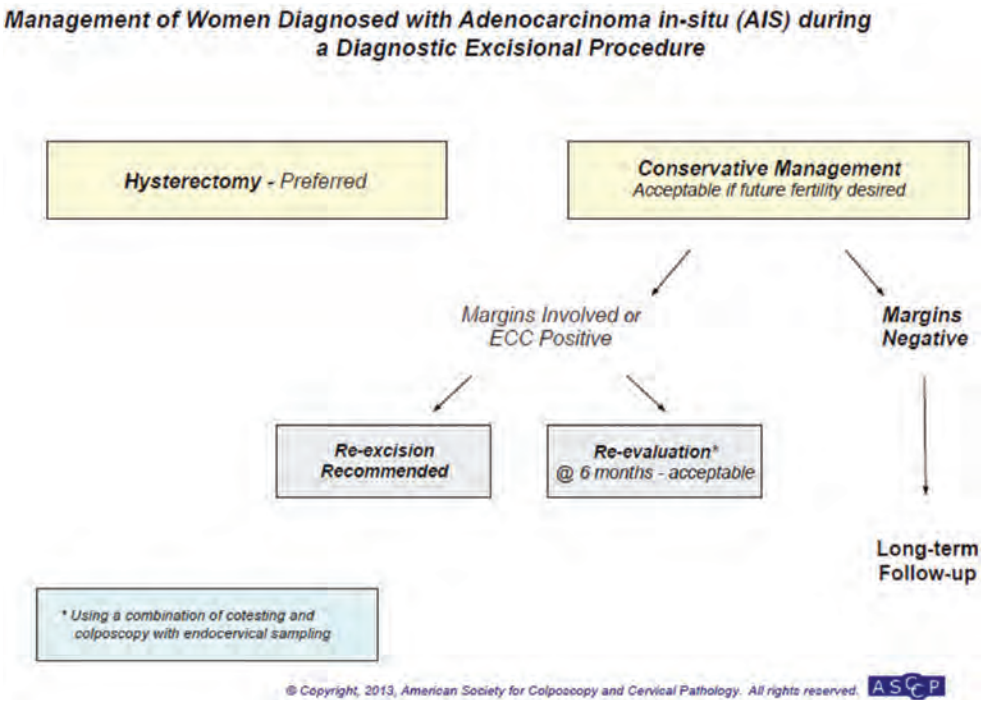

FIGURE 5.18 Management of women diagnosed with adenocarcinoma in situ (AIS) during a diagnostic excisional procedure. (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

including iodine allergy and anticoagulation. Pregnancy should be ruled out because an ECC should not be performed in this case. Good visual examination of the vulva and perineum, a speculum exam of vagina and cervix, and a bimanual exam to rule out obvious pelvic pathology should also be part of every patient visit for colposcopy. If the Pap test was more than 6 weeks ago, it can be repeated because many HPV infections resolve over time.

Colposcopy is performed with the patient in the dorsal lithotomy position using a standard speculum. First, a cotton swab with normal saline is applied to the cervix to clear any mucus and debris. This application facilitates the visualization of hyperkeratosis (white epithelium seen before the application of acetic acid) and allows for biopsy of such areas. Atypical vessels can also be seen with saline alone, often in conjunction with the green filter on the colposcope. These "corkscrew"-like vessels can be the hallmark of invasive cancer (Fig. 5.19).

Second, 3 or 5% acetic acid is liberally applied to the cervix. After 30 seconds, the cervix should be carefully inspected under low-power and high-power colposcope. Abnormalities commonly seen include acetowhite epithelium (due to abnormal intracellular keratin and protein agglutination, as well as cellular dehydration) suggestive of both low- and high-grade dysplasia (Fig. 5.20), and vascular abnormalities such as mosaicism and punctation (Fig. 5.21). These two findings often result from the capillary proliferative effect

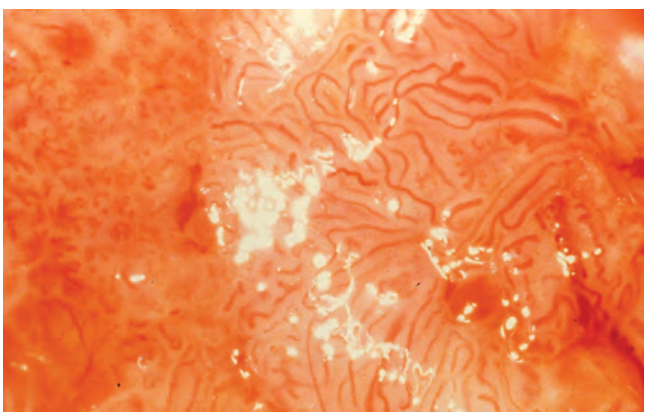

FIGURE 5.19 Colposcopic view of "corkscrew" (atypical) vessels. (Courtesy of Matthew A. Powell, MD.)

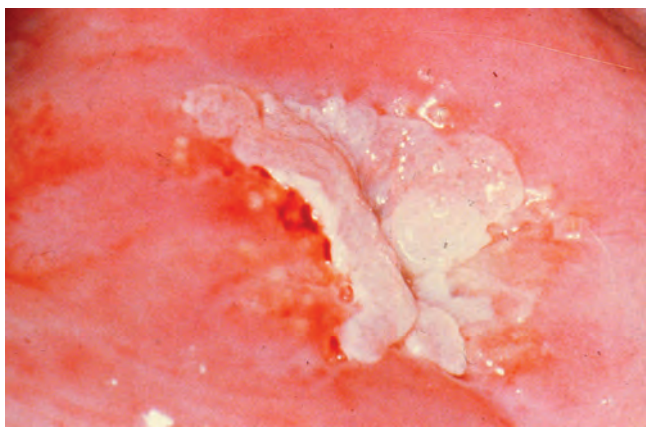

FIGURE 5.20 Colposcopic view of acetowhite epithelium. (Courtesy of Matthew A. Powell, MD.)

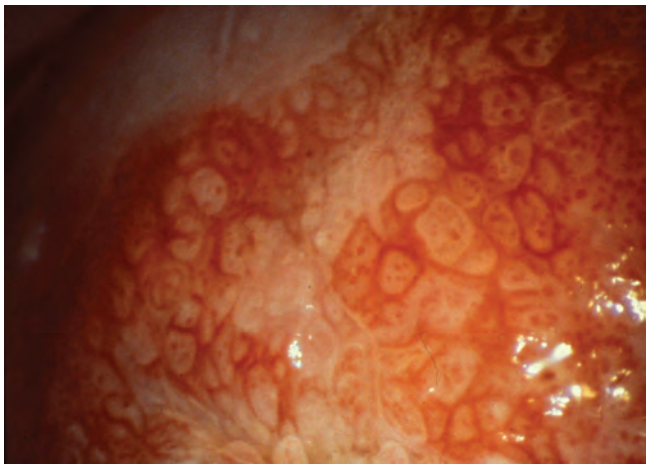

FIGURE 5.21 Colposcopic view of mosaicism and punctation. (Courtesy of Matthew A. Powell, MD.)

of HPV and of tumor angiogenesis factor. Although acetowhite epithelium and mosaicism/punctation may also be seen in association with benign processes such as inflammation and normal metaplastic transformation, biopsy of such lesions is always recommended.

Third, Lugol iodine may be applied to the cervix and/or the vaginal walls (Fig. 5.22). This solution is particularly useful when looking for a vaginal lesion because normal ectocervical and vaginal squamous epithelium stains dark brown with its application, whereas columnar, squamous metaplastic or dysplastic epithelium appears light yellow. This effect is due to the presence of glycogen in normal squamous epithelium. Lugol iodine may be helpful in detecting subtle dysplastic lesions on the cervix and especially in the vagina, although both a high false-negative and a high false-positive rate have been described.

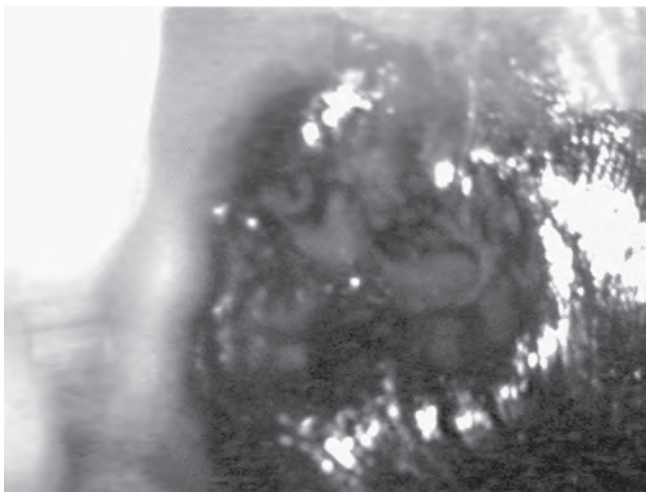

FIGURE 5.22 Colposcopic view of cervix with Lugol's iodine. (Courtesy of Matthew A. Powell, MD.)

Colposcopy is deemed satisfactory if the entire TZ is visualized because the incidence of dysplasia above this junction is minimal. Almost all cervical neoplasia arises in the TZ, which is defined as the junction of the squamous (ectocervical) and columnar (endocervical) cells. Use of a Q-tip or endocervical speculum (more traumatic) can help visualize the TZ.

ECC assesses the portion of the endocervical canal not visualized by colposcopy. It is indicated for patients with ASC-H, HSIL, AGC, or AIS. It is also indicated for ASCUS and LSIL if no lesion is visible. It is contraindicated in pregnant women. This is done by scraping the canal 360 degrees with a long, straight curette and removing any extra cells/blood at the external os with a cytobrush or ring forceps.

All colposcopic findings should be recorded on a schematic drawing labeled such a fashion that another health care provider can easily reconstruct the location and extent of all visualized lesions, their appearance, biopsy sites (numbered as on the face of a clock), and the adequacy of the exam. Photographic or video documentation is also helpful. Some common abbreviations include the following:

1. TZ – transformation zone
2. WE – white epithelium
3. L – leukoplakia (thick WE)
4. SM – squamous metaplasia (HPV changes)
5. P – punctation
6. M – mosaicism
7. AV – atypical vessels
8. E – ectopy
9. AS – adenosis
10. NC – Nabothian cyst

Visual Inspection Methods

Direct visual inspection of the cervix following application of 3 to 5% acetic acid or with Lugol iodine has been attempted as an alternative to Pap smear in resource-poor settings. A study from the University of Zimbabwe compared the performance of visual inspection with acetic acid and the Pap smear in the hands of midlevel providers and established direct estimates for sensitivity, specificity, and positive and negative predictive value for the detection of high-grade dysplasia with the technique.[77] These estimates are considered direct because all women testing negative or positive on screening were offered colposcopy and biopsy as indicated. In this study, visual inspection had sensitivity for HSIL of 76.7% compared with 44.3% sensitivity for cytology and specificity of 64.1% compared with 90.6% specificity for cytology for the detection of high-grade dysplasia. The lower specificity has been ascribed to a high rate of sexually transmitted diseases in the population and to the limited training of some of the providers performing the screening. The most important observation is the high

negative predictive value of this simple and inexpensive technique, thereby eliminating the need for further testing in those patients that screen negative.[78] This approach was further supported by a review in 2003; the long-term effectiveness of this approach in reducing morbidity and mortality from cervical neoplasia remains to be established.[79]

Cervicography

This employs standard photography of cervix, which can then be magnified and interpreted anywhere in the world. This technique has poor sensitivity and therefore is not recommended for primary screening but as an adjunct.

Speculoscopy

This method of visual inspection uses a chemiluminescent light source named Speculite (Trylon Corp., Torrance, CA) to evaluate abnormal areas on the cervix. A handheld optic device provides four to six times magnification of the cervix after the application of acetic acid.

Treatment of Cervical Dysplasia

There are a variety of treatment options, and no one treatment is superior to another. Options include excision procedures (LEEP, cold-knife cone) and ablative procedures (laser or cryo). One advantage of excision procedures is that the disease margins are visible. Disease margins are linked to prognosis, with negative margins usually being curative.[80] Each has its own advantages and disadvantages, and one treatment may be better suited to a patient at a given time because of age, anatomy, type of dysplasia, medical history, or a variety of other reasons. See Table 5.4 for indications for excision and contraindications for ablation.

TABLE 5.4 Indications for Excision and Contraindication for Ablation

Excision is indicated for the following:

1. Suspected adenocarcinoma in situ
2. Suspected microinvasion
3. Lesions extending into the canal
4. ECC showing CIN or glandular abnormality
5. Recurrence after treatment of high-grade lesions
6. Colposcopist unable to rule out invasive disease
7. Unsatisfactory colposcopy (except in pregnancy)
8. Lack of correlation between Pap and colposcopy/biopsies (consider review of material)

Ablation is contraindicated if:

1. Patient is noncompliant
2. Colposcopy has not been performed or is not satisfactory
3. Glandular or invasive lesion suspected
4. ECC identifies *any* CIN

ECC, endocervical curettage; CIN, cervical intraepithelial neoplasia.

Hysterectomy is not a primary treatment option because it is associated with increased morbidity. Furthermore, invasive cancer needs to be ruled out so that a simple hysterectomy is not performed in a patient with invasive carcinoma.

Ablative Treatment

Ablative treatment strategies generally do not yield a histologic specimen so cancer could be missed. It is therefore extremely important to make an accurate tissue diagnosis of dysplasia and to rule out any possibility of invasive disease prior to proceeding with ablative treatment. Again, using HPV typing to look for types 16 or 18 can be useful in this scenario. Ablative methods do not increase the risk of preterm birth (PTB) or preterm premature rupture of membranes (PPROM).[67]

Cryotherapy and laser ablation are the most commonly used methods in the United States, but cold coagulation and diathermy are used elsewhere. Tissue penetration needs to be 5-mm deep to be effective. Pretreatment with prescription strength nonsteroidal anti-inflammatory drug along with a cervical or paracervical block is effective for cryotherapy and cold coagulation, whereas regional or general anesthesia may be required for laser or diathermy. Although routine cultures and antibiotic prophylaxis are not required, treatment should not be performed on patients with active cervicitis or who are menstruating.

Cryotherapy is a treatment that is cost-effective and easily performed in the outpatient setting. It is well suited for persistent biopsy-confirmed low-grade lesions that are less than 3 cm in diameter and do not extend into the endocervical canal. It is also more commonly performed on younger patients. Cryotherapy leads to destruction of the TZ via cryonecrosis using the evaporation of liquid refrigerants, most commonly carbon dioxide or nitrous oxide. Compressed gas is allowed to expand through a small jet producing an ice ball at the tip of a metal probe, which is brought in contact with the surface to be destroyed. Cell death results from crystallization of intracellular water at −20 to −30°C. To achieve a 5-mm depth of freezing, the probe must cover the entire TZ and produce a total lateral spread of freeze of 7 mm. Creasman et al.[81] advocates a freeze-thaw-freeze technique (3-5-3 minutes) with a repeated freeze after the tissues have visually thawed from the first freeze. With this technique, he observed a decrease in failure rates from 29 to 7%. Other investigators claim similar success with only one freeze. It is important to warn the patient of a watery, foul-smelling discharge after cryotherapy. If it persists at the 14-day follow-up, the necrotic tissue can be removed with ring forceps.

Carbon dioxide (CO_2) laser vaporization should only be used as ablative treatment by physicians with specialized training. Proper eye wear, nonreflective specula, wet towels, and nonpaper drapes are all essential safety

equipment. The CO_2 laser is mounted on a colposcope and controlled via a micromanipulator that controls the beam. The surgeon can adjust spot size, power, and mode settings. The entire TZ must be visualized with acetic acid or Lugol iodine prior to initiating laser treatment. The power density needs to be 600 to 1200 W per cm^2. There are several techniques, but Flowers and McCall[82] recommend the following conditions to maximize the success of the procedure: (a) destruction of the lesion to a visual depth of 5 to 7 mm ensures the treatment of glandular involvement; (b) a 5-mm visible width beyond the lesion is recommended; (c) a continuous tissue exposure mode setting should be used; and (d) if the equipment permits, high-power settings of at least 20 to 25 W or higher should be used to minimize lateral thermal damage. The patient can be given local anesthesia via a paracervical block. Also, use of a defocused beam and/or vasopressive injectable agents can control bleeding, as can silver nitrate or ferric subsulfate (Monsel). If used appropriately, laser vaporization can be very effective in treating cervical dysplasia with failure rates of less than 5%.

Cold coagulation is a popular ablative treatment in Europe. Despite its name, it uses a 100°C Teflon probe that is directly applied to the cervix. Two to five applications of less than a minute each per treatment lead to destruction of the TZ. Reported failure rates of this method are around 7%, and the procedure is short, pain free, and relatively inexpensive.

Diathermy uses an electrocautery needle to destroy cervical tissue. It is usually performed in an operating room (OR) suite with regional anesthesia. At approximately 30 to 35 W, the needle is passed into and out of the cervix multiple times, ablating the TZ. A spatula or ring forceps can remove the tissue. Usual electrocautery precautions apply.

Excision Treatment

Excision treatments or conization/cone biopsy can be performed with electrocautery (most common), a knife, or a laser. The goal is to remove the entire TZ, and each method is equally effective. Conization is the gold standard for treating CIN because these procedures produce pathologic specimens to confirm the initial diagnosis and delineate the margins of excision, which are prognostic. As previously stated, however, the risk of PPROM and PTB are somewhat increased, as is the risk of bleeding complications. See Table 5.4 for indications for excision.

LEEP, also known as large loop excision of the transformation zone (LLETZ), is the preferred method in most cases. It is easily done in the ambulatory setting, is effective, fast, low-risk, and inexpensive. Furthermore, most studies agree that difficulty in interpreting margins secondary to cautery artifact is rare and is easily outweighed by the many advantages of the procedure.[82]

LEEP can be performed with local anesthesia via a paracervical block. Bleeding may occur in about 2 to 5% of patients and is rarely heavy. Similarly, infection rates are lower compared with cold-knife conization. Cervical incompetence and stenosis are equally rare (less than 1% of patients), although they remain an important part of the informed consent for the procedure.

Prior to performing a LEEP, the patient should undergo colposcopy as is required before any other excision procedures. Typical electrocautery precautions, such as a plastic-coated instruments and a grounding pad, are required. The speculum is attached to suction to evacuate smoke, and vaginal sidewall retractors may be used to achieve optimal exposure of the cervix and minimize the risk for thermal injury to the vaginal fornices. Depending on the size of the lesion, the correct size loop is chosen, and the cervix is anesthetized. It is important to ensure the patient has a grounding pad attached to her thigh. The electrosurgical generator should be set to 55 to 60 W of pure cutting or blended current. The blended current provides better hemostasis but also produces more artifacts within the specimen. The surgeon can control the generator with the handle of the loop and excises the specimen with the loop perpendicular to the cervix either from side to side or from top to bottom. A visible margin of 2 mm should be left next to the lesion of interest, and a depth of approximately 5 to 7 mm should be achieved. Larger lesions may require more than one pass. Also, if a true cone biopsy is required, the surgeon can switch to a smaller loop and excise an additional endocervical region giving the two specimens combined a "top hat" configuration. Bleeding of the LEEP bed is controlled with electrocautery or with the use of a ball electrode and/or the application of Monsel solution. Patients are placed on pelvic rest for 2 to 4 weeks after the procedure.

Some physicians still prefer cold-knife conization for certain clinical scenarios, such as AGC favor neoplasia or endocervical AIS, although operator experience in conization versus LEEP should be considered. Cold-knife conization is almost exclusively performed in the OR usually under general anesthesia secondary to patient discomfort and the risk of bleeding. The vagina and cervix should not be prepared because this may affect the pathologic interpretation. After colposcopic examination (if practical), lateral sutures at 3 and 9 o'clock are shallowly placed for traction and hemostasis. Lugol or acetic acid can be applied to help visualize the TZ. A tenaculum or Allis clamp can be placed anteriorly (and posteriorly if space allows) to help manipulate the cervix. The portion of the cervix is infiltrated with a vasopressive agent lateral to the planned incision line, and the endocervical canal is sounded to determine length and direction of the cone (can be left in place as a guide). The cone-shaped specimen is then excised using a no. 11 scalpel after tagging it at 12 o'clock with a suture for proper orientation. Allis clamps may be

placed on the specimen side (but not onto the TZ) of the cervix to facilitate deeper excision. Mayo scissors can be used to deepen the cone and to cut the base. ECC is then performed. Cautery (which also aids further destruction of abnormal cells) and Monsel can be used for immediate hemostasis. Also, to reduce the risk of menstrual symptoms, stenosis, and unsatisfactory colposcopy, a nonsuture technique can be used for hemostasis. This is done by rolling up a piece of absorbable hemostat (Surgicel), placing it into the cervical canal and tying the stay sutures over it. The patient should be advised that a dark ball of material will come out of the vagina in the next week or two.[83] Hemostasis can also be achieved by using modified Sturmdorf sutures (two running sutures alternating from outside to inside along the anterior and posterior rims, tied at 3 and 9 o'clock).

Advantages of this technique include its technical simplicity and superior specimen quality. Disadvantages of cold-knife conization compared to other methods include cost of using an OR, higher risk of bleeding and infection, and higher incidence of cervical insufficiency and stenosis.

Laser conization should only be performed with specialized training of both the physician and staff. The physician should also have experience in cold-knife conization because many of the principles are the same. It is usually performed under regional/general anesthesia in the OR. As for any laser procedure, proper eye protection, drapes, and instruments are required for patient safety.

After wet towels are placed on the patients thighs, the cervix is injected and sutures are placed as discussed earlier. Under colposcopic visualization, a dotted margin is made 1000 to 1500 W per cm^2 around the outer limit of the TZ and the inner margin planned for ablation. The planned ablation is divided into quadrants. Using a power density of 500 to 1000 W per cm^2, the outer margin is ablated circumferentially to a depth of 5 to 7 mm. Changing the power to a smaller spot size of 0.5 to 1 mm (1000 to 1500 W per cm^2), the outer margin of the cone is circumferentially deepened. Skin hooks, tenacula, and the lateral sutures are used to get the desired cone depth. Mayo or Jorgenson scissors are used to cut the base. ECC is then performed. Hemostasis can be achieved by decreasing the power density on the laser of by the methods previously mentioned.

Advantages of laser include healing with minimal distortion, good hemostasis, and specimen quality. Disadvantages include that it is technically difficult, more costly, and has the potential for serious complications (fire) without proper training and precautions.

PREVENTION OF HUMAN PAPILLOMAVIRUS INFECTION BY THE HUMAN PAPILLOMAVIRUS VACCINE

The successful development and application of a preventive vaccine against HPV infection represents the single most important milestone in the prevention of cervical cancer since the introduction of the Pap test. HPV types 16 and 18 cause 70% of cervical cancer and 72% of anal cancers. Additionally, types 6 and 11 cause 90% of genital warts. Two vaccines, Cervarix (a bivalent vaccine against HPV 16 and 18) (Glaxo Smith Kline Biologicals, Rixensart, Belgium) and Gardasil (Merck and Co., Whitehouse Station, NJ, USA) (a quadrivalent vaccine against HPV 6, 11, 16, and 18) were approved by the FDA in 2006 and 2009, respectively, and have been extensively studied and used in the United States and in nearly 100 other countries. Currently, the vaccines are indicated for all females between the ages of 9 and 26 years for the prevention of cervical, vulvar, and vaginal dysplasias (Table 5.5). The vaccine is administered in three doses; the second dose follows the first after 1 month and the final dose 4 months after the second (months 0, 2, and 6). Cervarix differs slightly in the schedule because it is given at 0, 1, and 6 months. The long-term immunogenicity and efficacy of Gardasil has been assessed in multiple double-blind, randomized controlled trials. In females with no virologic evidence of HPV infection, prevention of CIN 2 or other anogenital disease approached 100%. Even in women who were sexually active, studies have shown a significant reduction of HPV-related disease.[84,85] A large, multinational prospective, double-blind, placebo-controlled trial, the PApilloma TRIal against Cancer In young Adults (PATRICIA) study demonstrated similar efficacy for Cervarix. These studies underscore the importance of universal mass vaccination against HPV infection regardless of sexual debut.[86] Additionally, both vaccines demonstrated partial protection against non-HPV vaccine types.

A recently completed observer-blind study[87] compared Cervarix and Gardasil regarding immunogenicity and safety 1 month following completion of the three-dose vaccination course. Virtually, all the participants (except two) between 27 and 35 years of age vaccinated with Gardasil developed antibodies. The geometric mean titers of antibodies ranged from 2.3- to 4.8-fold higher for HPV-16 genotype and 6.8- to 9.1-fold higher

TABLE 5.5 Indications for Human Papillomavirus/Cervical Cancer Vaccine (Gardasil) in the United States

Indicated in all girls and women between the age of 9 and 26 years for the prevention of the following:

- Cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11 and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18
- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)
- CIN grade 1
- Vulvar intraepithelial neoplasia (VIN) grade II and grade III
- Vaginal intraepithelial neoplasia (VAIN) grade II and grade III

HPV, human papillomavirus.
From http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM094042. Accessed December 2, 2013.

for HPV-18 genotype among patients treated with Cervarix compared to the Gardasil-treated cohort. The long-term significance of this observation in maintaining the immunogenicity and the potential benefit needs to be determined, however. The heightened immune response to Gardasil is expected to last for at least 20 years following vaccination according to one mathematical modeling study.[88] To date, this data provides the most compelling evidence for successful prevention of a potential malignancy in women.

Gardasil has demonstrated an immunologic response and a reduction in genital warts in large, randomized double-blind trial of 4065 males, of which 602 had sex with male partners.[89] Cervarix has also demonstrated 100% immunogenicity in a small Finnish study.[90]

Side effects of the vaccine are minimal and are mostly commonly local injection site reactions. For a full list of reactions, see the package inserts.

MANAGEMENT OF VAGINAL, VULVAR, AND ANAL INTRAEPITHELIAL NEOPLASIA

Vaginal intraepithelial neoplasia (VAIN) is presumed to have a similar natural history as CIN although it has been less extensively studied.[91-94] The incidence of VAIN is difficult to assess given its rarity, although one study placed it at 0.2 to 0.3 cases per 100,000 women,[95] and it accounts for approximately 0.4% of all lower genital tract neoplasia. Like vulvar and cervical dysplasia, an association between HPV and VAIN has been established. In the past, many women underwent hysterectomy as excision treatment for high-grade dysplasia, but VAIN was noted to develop in about 5% of these women postoperatively, usually at the vaginal cuff suture line.[96] HPV and high-risk sexual behavior have been implicated in its etiology.[97] Thus, risk factors are presumed to be the same as for cervical dysplasia, as is explained by the "field effect" of the lower genital tract.

Similar to cervical dysplasia, VAIN is reported as VAIN I through III. The progression of VAIN to invasive cancer has been less well established. Only very limited series have been published reporting an overall progression risk to cancer of 9%, with 13% persistence and 78% spontaneous regression.[97] Some investigators report that almost 30% of patients undergoing an excision procedure for VAIN III were found to have underlying cancer.[97]

The diagnosis of VAIN is made by vaginal colposcopy (Fig. 5.23). Acetic acid should be used, and care must be taken to achieve optimal exposure of the sometimes redundant vaginal vault in its entirety. Lugol iodine may also be helpful. VAIN can be both unifocal or multifocal with discrete or coalescent lesions. The most common reason to perform colposcopy of the vagina is a posthysterectomy Pap smear of at least ASCUS. Any suspicious-appearing lesions should be biopsied. Scarring or involution of vaginal tissue during closure of the vaginal cuff at hysterectomy can sometimes obscure the vaginal cuff area, precluding visual identification of a lesion. Therefore, in the absence of an identifiable lesion during vaginal colposcopy, it is sometimes necessary to excise a cuff scar or extensively biopsy the vaginal cuff area.

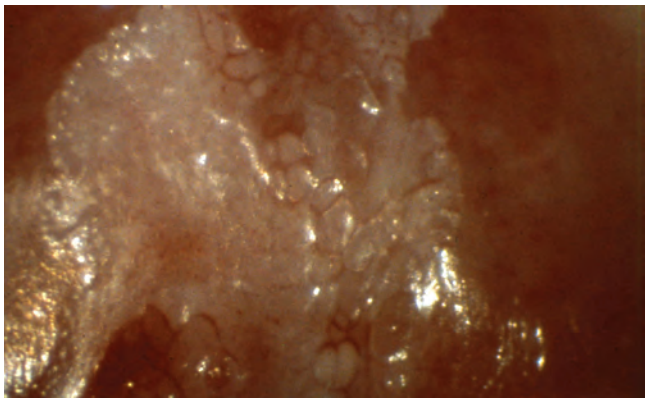

FIGURE 5.23 Colposcopic view of vaginal intraepithelial neoplasia. (Courtesy of Matthew A. Powell, MD.)

VAIN I should be followed, but the treatments for VAIN II to III include ablation, excision, chemotherapy, or even radiation. Although it is the generally preferred method for small lesions, optimal depth of ablation and success rates are variable with CO_2 laser vaporization in the literature. Thus, it is recommended that an experienced clinician perform the procedure. Ultrasonic surgical aspiration may be associated with less pain and scarring.[98]

Topical 5-fluorouracil (5-FU) cream has also been advocated as a treatment option for VAIN. Although the failure rates are similar to other techniques, this approach is associated with considerable side effects like burning and ulceration. Some investigators report particularly high failure and recurrence rates with 5-FU alone and prefer combining this topical agent with subsequent surgical excision. Imiquimod (Aldara) applied three times per week for 8 weeks is associated with a cure rate of 70%.[99] Larger studies are needed, however.

Excision in the form of upper vaginectomy is the treatment modality with the highest reported success rates. It affords a specimen for review but can also lead to shortening of stenosis of the vagina. An experienced surgeon using the OR mitigates potential risk of injury to the bladder and rectum during this procedure. Again, some feel that pretreatment skinks the lesion and makes the epithelium looser. Overall cure rates of 94% have been reported among patients with VAIN after a combination of surgical ablation and topical application of 5-FU were combined.[97]

Because of its high morbidity, intracavitary radiation is reserved for patients that have failed treatment, have extensive multifocal disease, or who cannot undergo surgery.

Vulvar intraepithelial neoplasia (VIN) was first described as a precancerous dermatosis by Bowen in 1912.[100] Invasive vulvar cancer represents 6% of all female reproductive cancers and 0.6% of all cancers affecting women.[101] It is more common in immunocompromised and postmenopausal women but can also be seen in healthy younger women. Risk factors are similar to those associated with cervical dysplasia, and HPV-16 is the most commonly associated HPV subtype. A previous history of lichen sclerosus and other benign disease of the vulva has also been an associated risk factor. Smoking is a significant risk factor for both cervical and vulvar cancer. A significant association has been established between VIN, CIN, and VAIN because up to 50% of patients may have either of this diseases as well.[102,103]

The classification of VIN underwent significant revision in 2004 by the International Society for the Study of Vulvar Diseases (ISSVD). The previous system of describing VIN as three separate entities (VIN I, VIN II, and VIN III) was abandoned in favor of two categories: VIN usual type and VIN differentiated type. Given the significant discrepancy between pathologic interpretations of VIN I, this new system has been adopted.[104] VIN usual type is an HPV-dependent lesion and generally represents a high-grade (previously VIN II and VIN III) lesion. This subtype tends to have a basaloid or "warty" appearance consistent with HPV infection.[105] VIN differentiated type usually occurs in older women and in patients with precancerous lesions such as lichen sclerosus and is generally not associated with HPV infection. The use of the VIN I to III classification system, however, is still used at many institutions, and familiarity with both systems is important.

The most common presenting sign for precancerous disease of the vulva is pruritus. Most patients, however, are asymptomatic, and disease is noted during routine gynecologic examination. This key feature highlights the importance of a thorough external exam and survey of the external vulvar tissue. Lesions are unifocal or multifocal; can appear gray, white, or reddish in color; and may be raised or flat. Attention should be drawn to both the periclitoral area and area around the anus because these areas are often missed and can be primary sites of VIN and invasive cancer. Lesions are sometimes seen extending into the vagina or involving the urethra or anus. Acetic acid of at least 5% strength should be applied for 4 to 5 minutes, but it is not always helpful in diagnosing VIN, and any suspicious-appearing lesion should be biopsied. Similar to CIN and VAIN, VIN may regress spontaneously, persist or recur after treatment, or progress to invasive cancer. In the previous system, high-grade VIN (VIN II to III) has been associated with underlying occult cancer in about 8% of cases. Progression rates of 2 to 18% have been reported, however, in untreated cases. VIN is rarely left untreated, and most physicians would only allow for very brief periods of observation before proceeding with definite treatment.

Treatment can be either excision, topical, or ablative after the possibility of malignancy is ruled out. The most common forms of treatment include both CO_2 laser ablation and wide local excision. Laser ablation is preferred for smaller lesions in non–hair-bearing regions. Substantial amount of postoperative pain, slow healing process, and lack of a pathologic specimen are the limiting factors of this procedure. Wide local excision is preferred mode of therapy in multifocal disease. It allows for precise excision of such lesions and the pathologic assessment of margins. A 5-mm margin of uninvolved tissue is believed by most to be adequate for VIN diagnosis[96] whenever this is possible without compromising surrounding structures. For large lesions, skinning vulvectomy with the creation of skin flaps can be used, whereas for extensive multifocal disease, a combination of surgery and laser ablation is often recommended.

Topical treatment with 5-FU is associated with significant patient discomfort and variable success rates. It is thus rarely used for the treatment of VIN. Topical treatment with imiquimod (Aldara) has been shown in a few studies to be effective in the treatment of VIN. Van Seters et al.,[106] in a randomized controlled trial, examined 56 women with VIN II or III and found that in the imiquimod group, 81% of women experienced a decrease in lesion size of greater than 25%. Further, they showed that HPV is cleared from the lesion site in 56% of patients. Both results were statistically significant as compared to placebo controls.

Recently, the therapeutic efficacy of a vaccine containing nine HPV-16 E6 and four HPV-16 E7 synthetic peptides was tested in 20 patients with biopsy-proven grade III VIN.[107] All subjects were HPV-16 positive before therapy. The vaccine was administered three times at monthly intervals. At 12-month follow-up, 15 out of 20 patients had reported significant clinical response and 9 out of 15 patients had histologic resolution as well. Because it was suggested that HPV-16 infections are associated with impaired $CD4^+$ T-cell immunity, the HPV-16 specific $CD4^+$ T cells and interferon gamma were measured. After vaccination, regardless of the clinical response, 85% of the patients had circulating vaccine-induced HPV-16 specific T cells. The abundance of these T cells and expression of interferon gamma correlated with therapeutic response. Although these studies are encouraging, further studies are needed to evaluate the role of this vaccine as a therapeutic agent.

The anal, vulvar, and cervical epithelium share the same embryologic origins and are therefore subject to the same pathology. AIN is more common in patients with HPV infection, immunosuppression, and with a history of receptive anal intercourse, including the other common risk factors for HPV. The incidence of anal cancer in the general population has increased over the past

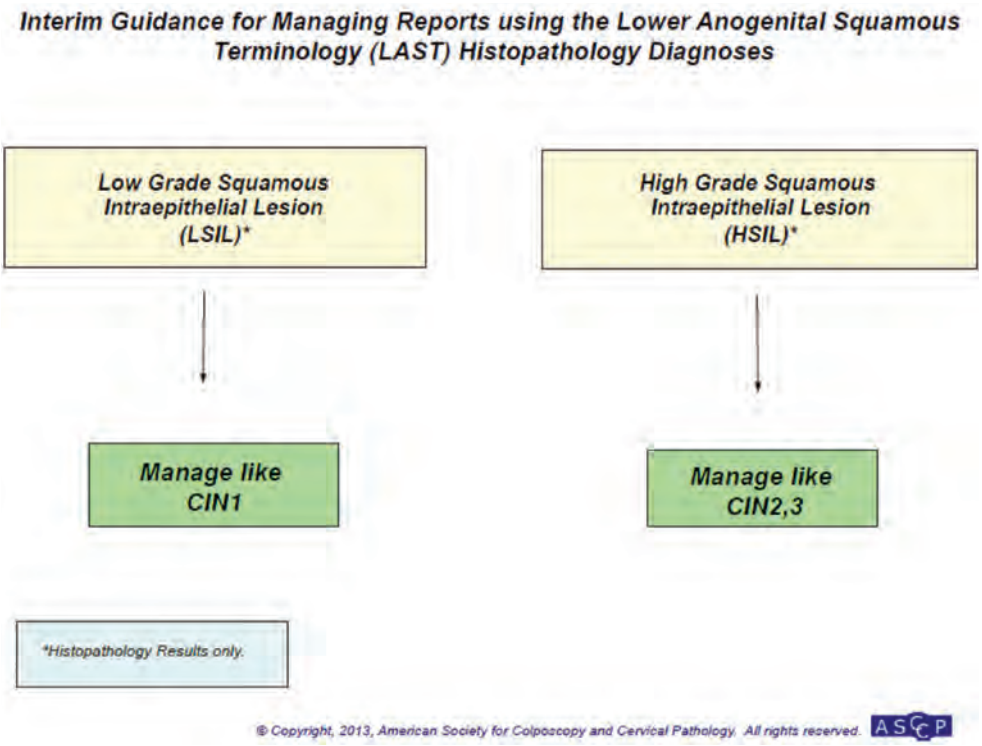

FIGURE 5.24 Interim guidance for managing reports using the lower anogenital squamous terminology (LAST) histopathology diagnoses. (Reprinted from *The Journal of Lower Genital Tract Disease*, Volume 17, Number 5, with the permission of ASCCP @ American Society for Colposcopy and Cervical Pathology 2013. No copies of the algorithms may be made without the prior consent of ASCCP.)

30 years, especially in women, which is roughly 1.5% per 100,000.[108]

Currently, there are no screening guidelines for AIN, but most authors agree on the following:

1. HIV-infected women
2. Women with a history of cervical, vulvar, or vaginal cancer
3. Chronically immunosuppressed women

Some also advocate screening women with a history of cervical, vulvar, or vaginal dysplasia.[109] Cell samples are obtained with a moistened synthetic swab and are fixed with liquid or convention preparations. Not surprising, HPV-16 is associated with the most anal cancer, so reflex typing is advised to help aid in management decisions. It is important for the patient to refrain from anal intercourse, douching, or enemas prior to screening. If cytology returns as ASCUS or greater, high-resolution anoscopy should be performed, which requires adequate equipment and training.[109] Management options include observation, topical therapy, infrared coagulation, and ablation, depending on the clinical scenario (Fig. 5.24).

In conclusion, the screening for cervical dysplasia has decreased in frequency to avoid harm to the patient. Likewise, management and treatment of dysplasia has trended to a more conservative approach. Screening, management, and treatment of AIN is emerging, but for all anogenital dysplasia, the association of high-risk human papilloma virus (HR-HPV) is the same. This association and the subsequent development of the HPV vaccine represent significant milestones in the overall health for women. Given these discoveries, gynecologists should continue appropriate screening for HPV and its related diseases while encouraging patients to become vaccinated.

CLINICAL NOTES

- Up-to-date information is available at http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm and http://www.asccp.org.
- The high-grade lesions (CIN 2, 3, or HSIL) are usually found in women aged 25 to 35 years, whereas invasive cervical cancer is typically seen after the age of 40 years.
- HPV infection accounts for 99.7% of cervical neoplasia.
- Risk factors for acquiring HPV include sexual behavior, increasing frequency of sexual intercourse, early age of first coitus, number of lifetime sex partners, the male partner's number of lifetime sex partners, age, ethnicity, HIV infection, and smoking or living with smokers.
- The relationship between HPV infection and subsequent development of anogenital neoplasia is so compelling that the possibility of HPV-negative LSIL

(continues)

as a distinct biological entity is now shown to be unfounded.

- Only 1% of treated CIN 3 will become invasive. Left untreated, however, 30% of these same lesions will become cancer over a 30-year period.
- Studies have shown liquid-based cytology to be better at providing an adequate specimen and detecting ASCUS, LSIL, and glandular abnormalities. This method is not better at detecting the clinically relevant HSIL.
- Added benefits of liquid-based cytology systems include the ability to perform "reflex" HPV testing and detection of other concurrent infections (gonorrhea, chlamydia, etc.).
- Multiple studies have shown the increased sensitivity of HPV testing compared to Pap smears, especially in the cases of CIN 3 or more and AIS.
- Patients younger than 21 years of age should not be screened by any modality regardless of sexual history.
- HPV testing as a primary screening modality in patients 21 to 29 years of age is not currently recommended because the rate of HPV infection is high in this age group. Additionally, these women should only be screened every 3 years with a normal cytologic history.
- HPV "cotesting" (HPV with cytology) is recommended in women 30 to 65 years of age. If negative, they can be screened every 5 years.
- HPV type 16 (HPV-16) causes 55 to 60% of cervical cancer. HPV-18 causes 10 to 15% of cervical cancers, including a greater proportion of glandular cancers. These subtypes can be specifically tested for on the cobas HPV test or Cervista 16/18 test.
- HPV reflex testing is especially useful for ASCUS, allowing referral to colposcopy for HPV-positive patients and surveillance for those without.
- A patient with normal cytology and a positive HPV test can be further investigated for types 16 or 18 to determine her need for immediate colposcopy versus repeat cotesting in 1 year.
- Women with ASCUS who are HPV negative can be screened again in 1 year.
- ECC in pregnancy is unacceptable.
- In general, any high-grade lesion warrants colposcopy and ECC.
- Women with all subcategories of AGC and AIS should undergo colposcopy with ECC with HPV testing. In women older than age 35 years or other risk factors for endometrial lesions, endometrial sampling is also recommended. Colposcopy can be performed initially or after the results of the endometrial and endocervical biopsies are known.
- Initial management of LSIL does not include any excision or ablative procedures because these are reserved for documented dysplasia.
- CIN 1 generally regresses in women with low-grade cytologic abnormalities.
- For HIV-infected women with well-controlled disease, the same follow-up protocols could be used as in noninfected women.
- Treatment is recommended for both CIN 2 and 3 because the risk of progression is high (except in young and pregnant women).
- Colposcopy is indicated for any cytologic test showing ASCUS with a positive HPV test (except young women) or persistent ASCUS, ASC-H, AGC, LSIL, HSIL, or suspicion for invasive disease.
- ECC assesses the portion of the endocervical canal not visualized by colposcopy. It is indicated for patients with ASC-H, HSIL, AGC, or AIS. It is also indicated for ASCUS and LSIL if no lesion is visible.
- There are a variety of treatment options for cervical dysplasia, and no one treatment is superior to another.
- Ablation is contraindicated if the patient is noncompliant, a colposcopy has not been performed or is not satisfactory, a glandular or invasive lesion suspected, or the ECC identified *any* CIN.
- Any laser treatment requires specialized training and equipment.
- Hysterectomy is not a primary treatment option because it is associated with increased morbidity. Furthermore, invasive cancer needs to be ruled out so that a simple hysterectomy is not performed in a patient with invasive carcinoma.
- To reduce the risk of menstrual symptoms, stenosis, and unsatisfactory colposcopy, a nonsuture technique can be used for hemostasis after cold-knife cone biopsy.
- In females with no virologic evidence of HPV infection, prevention of CIN 2 or other anogenital disease approached 100%.
- VAIN I should be followed, but the treatments for VAIN II to III include ablation, excision, chemotherapy, or even radiation.
- The most common presenting sign for precancerous disease of the vulva is pruritus.
- When diagnosing VIN, any suspicious-appearing lesion should be biopsied.
- High-grade VIN (VIN II to III) has been associated with underlying occult cancer in about 8% of cases.
- The incidence of anal cancer in the general population has increased over the past 30 years especially in women.

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CHAPTER 6

Sexually Transmitted Infections and Pelvic Inflammatory Disease

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Sexually transmitted infections (STIs) are still very frequent worldwide. Despite continuous progresses in treatment, screenings, prevention, and counseling, they are still on the rise in many developed countries and in the United States where about 1.6 million new cases occur each year.[1] Effectively diagnosing and treating symptomatic and asymptomatic patients as well as their sexual partners can prevent complications associated with STIs and reduce the risk of disease transmission. However, therapeutic measures are insufficient because there is currently no cure for some of the most prevalent STIs (e.g., genital herpes and human papillomavirus [HPV] infections). Preventive measures such as screenings, patient counseling, and pre-exposure vaccinations have demonstrated benefits in the management of STIs. This chapter details the diagnosis, treatment, and prevention of the major STIs and pelvic inflammatory disease (PID).

SCREENINGS AND PREVENTIVE MEASURES

The U.S. Preventive Services Task Force (USPSTF) recommends that sexually active women younger than 25 years of age (including adolescents) have systematic annual screening for chlamydia, HIV, and gonorrhea (USPSTF recommendations for STI screening available at http://www.ahrq.gov/clinic/uspstf08/methods/stinfections.htm). Routine screening for herpes is not recommended because of potential high false-positive rates in low-risk populations.[2]

Chlamydia and gonorrhea infection rates are highest among females aged 15 to 19 years because adolescents, particularly those younger than the age of 15 years, are at high risk of acquiring STIs. Although biological factors such as cervical ectopy and lower levels of secretory immunoglobulin A (IgA), a local protective antibody in cervical mucus, have been postulated to contribute to this susceptibility, the evidence is not conclusive.[3,4] Recurrent acquisition of STIs is common among adolescents, with many being reinfected within a few months of the index infection. It is estimated that 40% of the reported incidences of chlamydia and gonorrhea occur in adolescents previously infected with the organisms.[5]

In one study of sexually active adolescent women ages 14 to 17 years, 25% of the adolescents acquired their first STI (most commonly chlamydia) by the age of 15 years, and the median time interval between the first occurrence of intercourse and the first diagnosed STI was 2 years.[6] STI screening for urban adolescent girls is recommended within the first year of sexual intercourse. Most adolescents in the United States can consent to the confidential diagnosis and treatment of STIs without parental consent or knowledge. There are a few states that require parental notification.

Many screening interventions have demonstrated a decline in chlamydial infections and the incidence of PID.[7] Interval screening times for STIs vary. For patients with no history of an STI, the screening interval is based on changes in risk factor(s) or number of sexual partners. It is recommended that women with newly diagnosed chlamydial, gonococcal, or *Trichomonas* infections should be rescreened in 3 months to test for new asymptomatic infections. A patient's sexual history should be included in the screening process to assess individual risk factors for STIs (see Table 6.11 for the required components of a sexual history for STI screening).

Although the burden of STIs is found primarily in younger populations, STI screenings are also recommended for older women who engage in high-risk sexual behavior. Postmenopausal women may not perceive themselves to be at risk for STIs although there is evidence that STI rates are increasing among older adults. Recent studies have found that the number of STIs among people older than age 45 years in the United Kingdom nearly doubled from 1996 to 2003.[8] From 2004 to 2009 in the United States, the rates of chlamydia infections in women aged 45 to 54 years increased from 23 to 39.3 per 100,000 individuals, whereas syphilis increased from 4.6 to 8.5.[1,9]

Patient education and counseling are important tools for preventing STIs. Client-centered counseling in which a patient's personal risk factors, situations in which the risk(s) occur, and having the patient or client set personal goals are effective in STI prevention. Training in client-centered counseling is available through the Centers for Disease Control and Prevention (CDC)

STD/HIV Prevention Training Centers (http://www.stdhivpreventiontraining.org). Abstinence and a reduction in the number of sexual partners are also reliable methods to avoid STIs. Counseling that encourages abstinence from sexual intercourse during the course of therapy for an STI is recommended.

Consistent use of male condoms reduces the risk for some STIs, including chlamydia, gonorrhea, trichomoniasis, HSV-2, and HPV-associated diseases.[10] In one prospective study among newly sexually active women in college, consistent and correct condom use was associated with a 70% reduction in risk for HPV transmission.[11] Although data are limited, the female condom also reduces the risk of STIs.[12]

Although proper condom use is effective at preventing STIs, they are not 100% effective at preventing transmission. The rate of condom breakage has been reported to be 0.5 to 3.7% in several prospective studies, and inexperienced users may contribute to condom failure.[13,14] There are two general categories of nonlatex condoms available in the United States. The first type is made of polyurethane or other synthetic material, can be substituted for latex condoms by those with latex allergies, and provides protection against sexually transmitted diseases (STDs)/HIV and pregnancy equal to that of latex condoms.[15] Compared to latex condoms, pregnancy rates among women whose partners use polyurethane or other synthetic condoms are similar, but the polyurethane or other synthetic condoms are more expensive and are reported to have higher slippage and breakage rates than latex condoms.[16]

The second category of latex condom alternatives is natural membrane condoms (often referred to as natural or "lambskin" condoms). Lamb cecum is often the source for these condoms, and although the pores in these condoms do not allow sperm to pass through, they are more than 10 times the diameter of the HIV virus and 25 times the diameter of the HPV virus. Viral STIs can be transmitted despite use of these condoms, and they are not recommended for the prevention of STIs.[15]

Condoms lubricated with spermicides are no more effective than other lubricated condoms in protecting against the transmission of HIV and other STDs. Frequent use of nonoxynol-9 (N-9) may actually enhance susceptibility to HIV infection by causing a breakdown of the mucosal barrier.[17] Therefore, use of condoms lubricated with N-9 is not recommended for STD/HIV prevention.

The cervical diaphragm demonstrated effectiveness in reducing cervical gonorrhea, chlamydia, and trichomoniasis transmission in observational studies.[18] Diaphragms alone should not be relied upon for the prevention of HIV transmission. The vaginal contraceptive sponge offers some protection against cervical gonorrhea and chlamydia although use of the sponge has been associated with candidiasis. Vaginal spermicides containing N-9 are not effective in preventing cervical gonorrhea, chlamydia, or HIV.

Pre-exposure vaccination is one of the most effective methods for preventing transmission of several STIs. Hepatitis A virus (HAV), hepatitis B virus (HBV), and some types of HPV can all be effectively prevented with pre-exposure vaccination. Hepatitis A pre-exposure vaccination is recommended for men who have sex with men (MSM), intravenous drug users, and HIV-infected patients. Two vaccines against some types of HPV are available and are discussed more fully in Chapter 5, Abnormal Cervical Cytology and Human Papillomavirus. The 2006 Advisory Committee on Immunization Practices (ACIP) recommends universal hepatitis B immunization for all unvaccinated adults being evaluated for STIs. Vaccine trials for other STIs are being conducted.

Reporting and notification practices are instrumental in the management of STIs. All states require mandatory reporting of the major STIs to local and state health departments. Syphilis, gonorrhea, chlamydia, chancroid, acute hepatitis B and C, HIV, and AIDS are reportable diseases in every state. Reporting can be carried out by the provider and/or by the testing laboratory depending on state requirements. Clinicians should be aware of local reporting guidelines or should seek out local health departments or state STD programs for guidelines. Disease reporting can also assist in the management of sexual partners. When STI infection is suspected in a patient, all sexual partners should be notified, examined, and treated for the STD. According to the CDC, data are limited as to whether partner notification effectively decreases exposure to STDs or if it reduces the incidence and prevalence of these infections in a community.[1] Treatment of partners, however, does decrease the risk of reinfection for the patient, so providers should at least encourage persons with STDs to notify their sex partners and urge them to seek medical evaluation and treatment.[1] When a partner is unlikely to seek treatment for an STD, partner-delivered patient medication (PDPM) can be used. In three clinical trials, the PDPM approach resulted in reduced prevalences of chlamydia (20%) and gonorrhea (50%) at follow-up.[19–21] However, this approach has been criticized because the sexual partner does not receive counseling or screening for other STIs. Clinicians should be aware that PDPM is not legal in all states in the United States.

SEXUALLY TRANSMITTED INFECTIONS

Diseases Characterized by Genital Ulcers

In the United States, genital herpes is reported to be the most common ulcerative STI followed by syphilis. Other STIs characterized by genital ulcers include chancroid, lymphogranuloma venereum, and granuloma inguinale. Occasionally, primary infection with HIV or cytomegalovirus (CMV) can be associated with genital ulceration. More than one etiologic agent may be present

in genital, anal, or perianal ulcers, for example, herpes and syphilis. Painful ulcers are typically seen in genital herpes and chancroid, whereas painless ulcers are typically seen in syphilis, lymphogranuloma venereum, and granuloma inguinale; however, a clinical diagnosis cannot be made on this distinction. Approximately 25% of all patients presenting with genital ulcers will never have a specific etiologic agent identified. The CDC recommends that all patients with genital, anal, or perianal ulcers be evaluated with a serologic test for syphilis and a diagnostic evaluation for genital herpes; in settings where chancroid is prevalent, testing for *Haemophilus ducreyi* should also be performed. Evaluation for chancroid, granuloma inguinale, or LGV will be determined by the prevalence of these infections in the area where the STI was acquired, the risk profiles of the patient's sexual contacts, and the patient's travel history as well as those of their contacts. HIV testing should be performed on all persons with genital, anal, or perianal ulcers who are not known to have HIV infection. Further screening for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, HIV, and Hepatitis B and C is also recommended for patients with genital ulcers.

A diagnosis of any STI based only on the patient's medical history and physical examination is frequently inaccurate. Despite this, clinicians often empirically treat for the diagnosis considered most likely based on clinical presentation and history (including travel history) while awaiting laboratory results.

Herpes Simplex

Herpes simplex virus (HSV) infection is one of the most prevalent STIs with rare but serious medical consequences such as neonatal infection and an increased risk (two- to four-fold) of acquiring HIV infection when herpes simplex virus type II (HSV-2) is present.[22] Genital herpes is also associated with significant psychological and psychosexual morbidity and is a chronic, lifelong disease.[23] Around 50 million adults in the United States report a history of genital herpes infection.[24] Genital infection can be caused by either herpes simplex virus type I (HSV-1), associated with oral/facial lesions, or HSV-2. Both HSV-1 and HSV-2 can be transmitted to other mucosal sites or through abraded skin by direct contact with infected secretions or autoinoculation. Although the average incubation period after exposure is 4 days, the incubation period of HSV-1 and HSV-2 ranges from 2 to 12 days.[25]

The majority of HSV-2 infections are asymptomatic or undiagnosed because the infections are subclinical. However, intermittent viral shedding in the genital tract does occur and represents an opportunity for transmission. Because of this, the majority of genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs. The frequency of viral shedding is influenced by the serotype present, the type of infection (primary or nonprimary), and time elapsed since the primary clinical infection. HSV-2 infections are associated with more frequent and prolonged periods of shedding than HSV-1 infections.[26]

HSV-1 is typically transmitted during childhood via nonsexual contact. As with HSV-2, most HSV-1 infections are subclinical. Acquisition of genital HSV-1 appears to be increasing, however, because recent studies have shown that up to 30 to 40% of new genital infections among women may be caused by HSV-1, particularly in adolescent and young adults.[24,27] Studies show that genital herpes caused by HSV-1 is increasing in the United States as well as in other developed countries.[28,29]

Clinical Symptoms

HSV infections may be classified into four groups: primary initial infection, nonprimary initial infection, recurrent infection, and subclinical infection (asymptomatic shedding). A primary infection occurs when a person without antibodies to HSV-1 and HSV-2, that is, they were seronegative, becomes infected. Although the primary outbreak of herpes can be asymptomatic, clinical signs may appear within 2 to 14 days of contact. The clinical manifestations of primary genital HSV infection are highly variable and tend to be more apparent in women than men. Mucoepithelial lesions are present and may be multiple and bilateral, starting as papules, progressing to vesicles, and erupting in painful ulcers. In 2 to 20% of patients, extragenital lesions, for example, aseptic meningitis, urinary retention, and distant skin lesions are also present. Fever, headache, malaise, myalgia, dysuria, and even tender lymphadenopathy are often present. It takes an average of 19 days for complete resolution of the ulcerative lesions to occur.

Because primary herpes infection is often associated with a prolonged clinical illness with severe genital ulcerations, all patients with a suspected primary episode of HSV should be treated with antiviral therapy. Therapy begun within 72 hours of the appearance of lesions may decrease the duration and severity of the illness by days or weeks as well as the risk of complications.[30] Up to 25% of patients presenting with a first clinical episode of herpes infection have serologic evidence of a past HSV-2 infection, which was asymptomatic.[31]

Nonprimary initial infection refers to the acquisition of HSV-1 in a patient who has previously been infected with HSV-2 or acquisition of HSV-2 in a patient who has previously been infected with HSV-1. The symptoms of nonprimary initial infections may be less severe than primary infection and systemic symptoms, most likely because antibodies against one type of HSV infection afford some protection against the other.

After primary infection with HSV, the virus becomes latent in sensory nerve ganglion. Recurrent infections are the result of symptomatic and asymptomatic viral shedding when reactivated virus travels the sensory nerve

from a nerve ganglion to the mucoepithelial surface. Recurrent infections are less severe, more likely to be unilateral, lack systemic symptoms, and are of shorter duration than primary or nonprimary infections. In the first year after the latency period, untreated HSV-2 infection has a median recurrence rate of four episodes, whereas HSV-1 is associated with a median recurrence rate of one episode.[23] The frequency of recurrence depends on the severity and duration of the initial episode, the infecting serotype, and the host immune response. Trigger factors for recurrent outbreaks vary from person to person and can include fever, menses, emotional stress, or local trauma. Although systemic symptoms are uncommon, prodromal symptoms, including vulvar burning, tingling, itching, and hypersensitivity, may be present prior to the appearance of lesions. The length of viral shedding is shortened in recurrent infections, usually lasting 5 to 10 days without antiviral therapy. Antiviral therapy that is started within 24 hours of the first prodromal sign or symptom increases the likelihood that the recurrence will resolve without the development of lesions.

Asymptomatic viral shedding is very frequent in HSV-infected patients and has been found in both men and women with no evidence of genital lesions.[32,33] Viral shedding appears to be more frequent in people with symptomatic recurrences compared to those who are asymptomatic. In one study, persons with asymptomatic HSV-2 infection had a shedding rate of 10.2% compared with a rate of 20.1% among persons with symptomatic genital herpes.[33] Subclinical HSV shedding is the major cause of sexual transmission of HSV because infected persons are unaware that they have the infection or they are asymptomatic when transmission occurs.

Diagnosis

Diagnostic testing for HSV includes viral culture, polymerase chain reaction (PCR) assays, direct fluorescent antibody (DFA), and Tzanck preparation. Clinical diagnosis has a maximum sensitivity of 39% and results in a false-positive diagnosis in about 20% of patients; therefore, confirmatory testing using viral or serologic tests is required.[2,34] Cell culture and PCR are the preferred diagnostic tests for HSV. A swab taken from the base of a lesion (vesicles will need to be unroofed prior to obtaining the swab) may be tested for HSV using viral culture, HSV antigen testing, or PCR testing for HSV DNA. If a viral culture is taken, the specimen must be refrigerated and rapidly transported to the laboratory, and isolates usually grow within 5 days. Viral cultures have low sensitivity, especially for recurrent lesions or lesions that have already started to heal. Vesicles contain the highest viral concentrations in the first 24 to 48 hours after presentation. Although a positive culture is a definitive diagnosis, a negative culture does not rule out the diagnosis of HSV infection. PCR assays are more sensitive than viral culture, less dependent on transport situations, and are significantly faster than viral culture.[35,36]

For DFA testing, viral samples can be obtained from a vesicle by swabbing; however, scraping the base with a blade is preferable to increase the yield of infected cells. The specimen should be spread over the center of a glass slide that is then air dried, fixed, and sent to the laboratory for testing. Positive results using DFA testing may be obtained within 24 hours. The use of Tzanck preparation to detect cellular changes of HSV infection is neither specific nor sensitive (less than 50%) and should not be relied upon.

Type-specific and non–type-specific antibodies to HSV develop during the first several weeks to months of infection and persist indefinitely. Older assays that are still available for serologic testing for HSV may not accurately distinguish between HSV-1 and HSV-2. Health care providers using serologic testing for HSV infections should ask for serologic type-specific glycoprotein G (gG)-based assays to be done.[37,38] Lab tests and point of care testing using gG-based type-specific tests for the detection of HSV-2 antibodies are available. The sensitivities of these serologic tests to detect HSV-2 antibody vary from 80 to 98% and false-negative tests may occur, especially during the early stages of infection.[39] Immunoglobulin M (IgM) testing for HSV is not useful because it is not type-specific, and positive tests may occur during recurrent episodes of herpes.

Currently, routine screening for HSV-2 is not recommended because there may be a high false-positive rate in low-risk populations, and there are no formal guidelines on how to reconcile test results.[2] Hence, routine testing would create a great deal of uncertainty and confusion.

However, the type-specific serologic tests may be used to confirm a clinical diagnosis of genital herpes, particularly if a false-negative HSV culture is suspected. In addition, these tests can be used to diagnose atypical lesions or in patients with recurrent genital symptoms.[1] They are also used to detect unrecognized infection and to manage the sex partners of persons with genital herpes. The use of testing to determine HSV type has been suggested for pregnant women at risk of acquiring herpes in the third trimester, for monogamous couples seeking ways to minimize transmission, for the diagnosis of recurrent genital eruptions, and for identifying HSV as a risk factor for HIV transmission in high-risk patients.

Treatment

Antiviral chemotherapy for herpes simplex infection provides clinical benefits to most symptomatic patients. The CDC recommendations for antiviral treatment and prophylaxis are listed in Table 6.1. Empiric antiviral therapy is recommended for all cases of suspected primary HSV infection. Even in primary infection cases with mild clinical manifestations, antiviral therapy is recommended because these patients can develop severe or prolonged symptoms. The first clinical outbreak of

TABLE 6.1 Recommended Regimen for the Treatment of Genital Herpes Infections

First Clinical Episode—Recommended Regimens

Acyclovir 400 mg orally three times a day for 7 to 10 days *or*
Acyclovir 200 mg orally five times a day for 7 to 10 days *or*
Famciclovir 250 mg orally three times a day for 7 to 10 days *or*
Valacyclovir 1 g orally twice a day for 7 to 10 days

Recurrent Episodes—Recommended Episodic Regimens

Acyclovir 400 mg orally three times a day for 5 days *or*
Acyclovir 800 mg orally twice a day for 5 days *or*
Acyclovir 800 mg orally three times a day for 5 days *or*
Famciclovir 125 mg orally twice a day for 5 days *or*
Famciclovir 1000 mg orally twice a day for 1 day *or*
Valacyclovir 500 mg orally twice a day for 3 days *or*
Valacyclovir 1 g orally once daily for 5 days

Recurrent Episodes—Recommended Suppressive Regimens

Acyclovir 400 mg orally twice a day *or*
Famciclovir 250 mg orally twice a day *or*
Valacyclovir 500 mg orally once daily *or*
Valacyclovir 1 g orally once daily

Severe Primary Infection or Disseminated Infection

Acyclovir 5 to 10 mg/kg IV every 8 hours for 2 to 7 days or until clinical improvement, followed by oral antiviral therapy to complete at least 10 days total therapy.

From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010.* Atlanta, GA: U.S. Department of Health and Human Services; 2011.

herpes may require hospitalization for pain control and possibly bladder catheterization to treat dysuria secondary to sacral nerve root involvement. Dysuria can be treated by intermittent or indwelling bladder catheterization over the course of several days. In addition to topical anesthetics (e.g., viscous lidocaine) applied to the lesions, the use of oral or intravenous painkillers including analgesics and narcotics may be necessary. Other symptomatic measures include applying warm compresses and sitz baths for patients with severe dysuria secondary to multiple ulcerations.

Intravenous antiviral medication is indicated in severe primary outbreaks or in disseminated herpetic infections. The following clinical criteria during primary HSV infection warrant initiation of parenteral therapy:

- Central nervous system (CNS) disease such as aseptic meningitis, encephalitis, or transverse myelitis
- End organ disease including hepatitis and pneumonitis
- Disseminated HSV

To treat complicated HSV, the CDC recommends intravenous acyclovir (5 to 10 mg/kg) every 8 hours for 2 to 7 days or longer until evidence of clinical improvement, followed by oral antiviral therapy to complete at least 10 days of therapy.[1] In instances of impaired renal function, the dose of acyclovir will need to be adjusted. Oral treatment can be extended for more than 10 days if lesions are not completely healed. Topical therapy with antiviral drugs offers no/poor clinical benefit and should not be used.

Systemic antiviral drugs partially control the signs and symptoms of herpes episodes when used to treat recurrent clinical outbreaks or when prescribed as daily suppressive therapy. However, these drugs neither eradicate the virus nor affect the pattern of recurrences and risk of transmission once they are discontinued. Clinical trials have shown that acyclovir, valacyclovir (the valine ester of acyclovir with enhanced absorption after oral administration) and famciclovir provide equal clinical benefit in the treatment of genital herpes. Famciclovir may be less effective in suppression of viral shedding however.[40] Famciclovir and valacyclovir allow for less frequent dosing compared to acyclovir; however, acyclovir is less expensive. When oral antiviral therapy is initiated within 24 hours, the recurrence of lesions may be aborted or at least the duration and severity of symptoms decreases significantly. The initial suggested treatment duration for recurrent herpes was 5 days, but studies have shown that shorter treatment times with famciclovir (1000 mg twice a day for 1 day), acyclovir (800 mg three times a day for 2 days), or valacyclovir (500 mg twice a day for 3 days) are effective alternatives.[41-43] Topical therapy with antiviral drugs offers no clinical benefit and should not be used. Allergic reactions or other adverse effects with famciclovir, valacyclovir, and acyclovir are rare. A desensitization regimen for acyclovir has been described.[44]

After a primary infection or in instances of recurrent infection, antiviral therapy may be given as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Patients may choose to take episodic therapy at the first signs of a recurrent outbreak (prodromal symptoms) or they may opt for continuous suppressive therapy in case of frequent recurrences (i.e., at least six recurrences per year). Episodic therapy with acyclovir, famciclovir, or valacyclovir has shown to decrease the proportion of patients with outbreaks, reduce the duration of symptoms, and shorten the duration of viral shedding. Patients who self-initiate therapy receive a greater clinical benefit with episodic therapy than patients who initiate treatment within 48 hours of lesion appearance.

Suppressive therapy reduces the frequency of genital herpes recurrences by 70 to 80% among patients who have frequent recurrences (more than six clinical episodes per year), and many patients report no symptomatic outbreaks.[45] Daily antiviral therapy reduces viral shedding and the risk of transmission to an uninfected sexual partner. Patients taking suppressive therapy rate their quality of life higher compared to those on episodic therapy.[46,47] Valacyclovir, famciclovir, and acyclovir appear to have similar benefits in providing suppressive therapy.

Compared to episodic therapy, suppressive therapy has the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners.[48] In couples where there is discordance for HSV-2 infection,

suppressive therapy should be considered as part of an overall strategy for reducing transmission; consistent condom use and avoidance of sexual activity during outbreaks should also be observed.

Treatment regimens can be determined by the frequency of episodes, severity of symptoms, and whether the patient has an uninfected partner. Ease of administration and cost are important considerations for prolonged treatment.

Counseling regarding the natural history of genital herpes, sexual and perinatal transmission, and methods to reduce transmission is integral to clinical management. The goals of counseling are to help patients both cope and manage their infection(s) and prevent sexual and perinatal transmission. Counseling should include information about the natural course of the disease, the possibility of recurrences, the significance of asymptomatic viral shedding, and the availability of suppressive or episodic therapy. All patients with herpes should be counseled to inform their current (and any future) sex partners and to abstain from sexual activity with uninfected persons when prodromal symptoms or lesions are present. Patients should be informed that consistent and correct use of latex condoms may decrease transmission. Sexual partners should be informed that they may be infected even if they have no symptoms. (In instances where it is not known if the sexual partner is infected, type-specific serologic testing of the asymptomatic partners of persons with genital herpes can help determine whether such partners are already HSV seropositive or whether risk for acquiring HSV exists.) The risks of neonatal HSV infection should be explained to everyone diagnosed with HSV, including men. All patients with HSV-2 seropositivity are at increased risk for HIV acquisition and should be told this. They should also be informed that suppressive antiviral therapy does not reduce the increased risk for HIV acquisition associated with HSV-2 infection.[49,50]

Special Considerations

Pregnancy

Because of the potential for neonatal morbidity and mortality with vertically acquired infection, all pregnant women should be asked if they have a history of herpes or if their partners do. Approximately 1 to 2% of susceptible women acquire HSV during pregnancy and most new infections are asymptomatic.[51] Among women with a history of recurrent outbreaks, 75% will have at least one recurrence during pregnancy and approximately 14% will have prodromal symptoms or clinical recurrence at the time of delivery.[52]

The CDC recommends that pregnant women who are not known to be infected with HSV-2 should abstain from intercourse with men who have genital herpes during the third trimester of pregnancy.[1] Similarly, pregnant women who are not known to have orolabial herpes should avoid receptive oral sex from partners known to have orolabial herpes infections and genital exposure to HSV-1 during the third trimester.

Approximately 80% of infected neonates are born to mothers with no known history of genital herpes. The risk of transmission to the neonate from an infected mother is high (30 to 50%) among women who acquire genital herpes near the time of delivery and low (less than 1%) among women with histories of recurrent herpes at term or who acquire genital HSV during the first half of pregnancy.[51,53] For women with recurrent lesions at the time of delivery, the rate of neonatal transmission with vaginal delivery is 3%.[54] However, because recurrent genital herpes is much more common than primary herpes infection, the proportion of neonatal herpes infections acquired from a mother with recurrent herpes is substantial, and the majority of mothers lack histories indicating clinical evidence of genital herpes.

A primary outbreak in the first trimester of pregnancy has been associated with chorioretinitis, microcephaly, and in rare cases, skin lesions. Oral antiviral therapy may be administered to pregnant women with mild or moderate primary outbreaks to reduce the duration and severity of symptoms as well as to decrease viral shedding. For more severe primary outbreaks, oral therapy may be extended for more than 10 days if the lesions are not healed at that time. In severe or disseminated maternal infections, intravenous therapy may be administered.

The use of suppressive therapy late in pregnancy reduces the frequency of recurrent infection by 75%, and the rate of cesarean delivery for recurrent herpes is reduced by 40%.[55] Women with active recurrent herpes should be offered suppressive viral therapy (acyclovir 400 mg orally three times a day or valacyclovir 500 mg twice a day) at or beyond 36 weeks and continue until delivery. It should be noted that these doses are higher than those used in nonpregnant women for suppression. No data support the use of antiviral therapy among HSV seropositive women without a history of genital herpes.

Syphilis

Syphilis is a reportable STI in the United States. The majority of syphilis infections are seen in MSM, although increases occurred in heterosexual populations from 2001 to 2009.[1] The South accounts for about 46% of the national cases of primary and secondary (P&S) syphilis in 2010.

Syphilis is caused by the spirochete *Treponema pallidum* and is primarily acquired through contact with an infectious lesion. Only a few *T. pallidum* organisms are required to infect abraded skin. The lesions of P&S syphilis include chancres, mucous patches, and/or condylomata lata, all of which are highly infectious. The risk of infection to a partner of an infected person is approximately 30 to 33%.[56] Syphilis may also be spread by kissing or via contact with lesions on the lips, on or

in the oral cavity, or on the genitals. *T. pallidum* is very labile and syphilis cannot be spread through contact with inanimate objects such as toilet seats or sex toys.

Based on clinical findings, the infection is divided into (overlapping) stages: primary, secondary, latent, and tertiary. In primary infection, the lesions present as an ulcer or chancre at the primary infection site. Neurologic infection may present at any time after initial infection and may present clinically as cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities. In secondary infection, the manifestations may include skin rash, lymphadenopathy, or mucocutaneous lesions, to name a few. Tertiary infections present as cardiac or gummatous lesions.

Latent infections are those that are diagnosed by serologic testing alone and are classified as either early latent (infection acquired within the preceding year), late latent (infection acquired over a year ago), or latent syphilis of unknown duration. Patients with early latent infection are considered to be potentially infectious, whereas those with late latent infection are not likely to transmit the disease. Misclassification of latent syphilis is common. Although there have been proposals to distinguish early latent infection from late latent infection on the basis of nontreponemal titers, this is not a reliable distinguishing feature.[1]

All patients who have syphilis should be tested for HIV. In areas where the prevalence of HIV is high, patients with primary syphilis should be retested for HIV after 3 months if their initial HIV test was negative.

Clinical Symptoms

Syphilis has been called "the great imitator." It can present in patients at any stage with nonspecific symptoms. The trademark of primary syphilis is the chancre—a solitary, indurated, and painless ulceration that occurs at the site of inoculation of the spirochete after an incubation period of 10 to 90 days. The chancre is a 1- to 2-cm ulcer that is indurated with a smooth base and raised, firm borders. There is no exudate unless secondary infection occurs. There is little pain or bleeding if the lesion is scraped. The chancre may occur in the cervix, vagina, vulva, anus, or on nongenital sites such as the oropharynx. When the chancre is located on the cervix or in the vagina, it can go unnoticed by the patient. Thus, women may be unaware of the infection until serologic testing is performed. Multiple chancres can occur particularly in patients infected with HIV. The tissue destruction that occurs in syphilis is caused by the immune response to *T. pallidum*. If untreated, the primary chancre resolves spontaneously within 3 to 6 weeks. Although the mechanism of healing is unknown, local immune responses are believed to be responsible. The chancre represents the local, initial infection with syphilis, but during this primary stage of syphilis, widespread dissemination of the infection may occur.

In the absence of therapy, approximately 25% of patients will develop the secondary stage of syphilis 6 weeks to 6 months later. During secondary syphilis, the spirochetes multiply and spread throughout the body. Secondary syphilis is associated with a wide variety of symptoms but is often characterized by low-grade fever, malaise, lymphadenopathy, and rash. The primary chancre may still be present, particularly in HIV-infected patients.

Lymphadenopathy may be found in the posterior cervical, axillary, inguinal, and femoral regions. Nodes are tender, firm, and have a rubbery consistency. Epitrochlear adenopathy, a rare occurrence, should strongly raise suspicions for the diagnosis of syphilis.

The nature of the rash in secondary syphilis is variable. It may be macular, maculopapular, papular, or pustular. Nodular lesions may also be seen. With the exception of congenital syphilis, it is never vesicular. It may occur anywhere on the body including the palms of the hands and soles of the feet. Lesions may be present in areas closest to the primary chancre and are often scaly, red or reddish-brown, and measure 0.5 to 2 cm in diameter. In warm, moist areas of the body such as mucous membranes in the mouth and perineum, gray to white plaques called "condylomata lata" may develop. They are highly infectious as are mucous patches that may develop as silvery gray, shallow ulcerations with a raised red border. Patchy alopecia may be present on the scalp, eyebrows, or beard.

Severe complications from syphilis include syphilitic hepatitis, infiltrated or ulcerated gastrointestinal tract, anterior uveitis or panuveitis, synovitis, osteitis, periostitis, and renal involvement in the form of immune-complex glomerulonephritis or nephritic syndrome. During the secondary stage, there is hematogenous and lymphatic dissemination of the spirochete. If left untreated, the symptoms of secondary syphilis will resolve spontaneously.

An asymptomatic latent phase follows secondary syphilis and is variable in duration. The CDC defines early latent phase as latent infection acquired within 1 year, whereas the World Health Organization (WHO) defines early latent phase as infection of less than 2 years. Syphilis is sexually communicable by patients in primary, secondary, or early latent stages. The late latent stage is unlikely to be sexually contagious but can be transmitted to a fetus transplacentally. Latent syphilis is often misclassified. It has been proposed that latent syphilis be characterized as "high-titer" or "low-titer" syphilis; however, early latent syphilis and late latent syphilis cannot be distinguished based solely on titers in nontreponemal tests.[1]

If syphilis is untreated, approximately 25 to 40% of infected patients will develop tertiary syphilis. Clinical manifestations of tertiary syphilis may occur as early as 1 year or as late as 25 years after primary infection. Tertiary syphilis is characterized by the involvement and progressive destruction of the cardiovascular

system (often the ascending thoracic aorta), CNS, and/or the musculoskeletal system. Various organ systems may develop gummata (late benign tertiary syphilis). Cardiovascular syphilis typically occurs 10 to 30 years after initial infection and results in a dilated aorta and aortic valve regurgitation. A high-pitched "tambour" second sound may be detected upon physical examination and chest films often show a calcified ascending arch of the aorta not typical of arteriosclerotic disease. Syphilis may also involve the coronary arteries.

Neurosyphilis can occur during tertiary syphilis but may occur at any time during the course of the disease. Involvement of the CNS in early stages of syphilis may present as asymptomatic meningitis, symptomatic meningitis, and meningovascular disease; it is frequently seen in patients with concurrent HIV infection. Early neurosyphilis may also present as symptomatic meningitis, ocular neurosyphilis (most commonly, posterior uveitis), hearing loss (with or without tinnitus), and meningovascular syphilis which may present as an ischemic stroke in a young individual.

Currently, CNS involvement is the most common manifestation of tertiary syphilis, but it is also the most difficult to diagnose and to treat. Neurosyphilis is often divided into meningeal, vascular, and parenchymatous forms (the latter including tabes dorsalis and general paresis). The meningeal and vascular may occur together (meningovascular syphilis), is an inflammatory process, and is seen more frequently compared to the parenchymal forms. Meningovascular syphilis usually occurs within 10 years of infection (often between years 4 and 7) and may cause strokes. Unlike other causes of strokes, meningovascular syphilis may cause prodromal symptoms that may be present for months before the actual cerebral infarction. Stroke symptoms can be either acute or subacute in onset.[57]

Tabes dorsalis, or locomotor ataxia, occurs with syphilitic involvement of the posterior columns of the spinal cord and of the dorsal roots. The most frequent symptoms of tabes dorsalis are sensory ataxia and sudden onsets of severe, stabbing pain in the limbs, back, or face. The general paresis is a progressive, dementing illness. On physical examination, dysarthria; facial and limb hypotonia; intention tremors of the face, tongue, and hands; and reflex abnormalities may be seen. Pupillary abnormalities, for example, the Argyll Robertson pupil (the pupil does not react to light but accommodates, dilates imperfectly to mydriatics, and does not dilate in response to painful stimuli) may also be present. Many patients with neurosyphilis are asymptomatic.

Recommendations for lumbar puncture testing to ascertain CNS involvement in syphilis are in Table 6.2. The cerebrospinal fluid (CSF) abnormalities occurring in neurosyphilis include pleocytosis (45 white blood cell [WBC] per high-power field), low glucose (2/3 serum glucose), and elevated protein (445 mg/dL). In up to 4% of patients with symptomatic neurosyphilis, these tests may be normal.[58] False-positive Venereal Disease Research Laboratory (VDRL) testing of the CSF is rare but may occur if there is contamination of the specimen with blood. False-negative VDRL testing may occur in up to 70% of patients with neurosyphilis. Testing using CSF fluorescent treponemal antibody absorption (FTA-ABS) analysis is controversial, and its use has been discouraged because it may lead to the overdiagnosis of neurosyphilis. However, a reactive serum FTA-ABS with a nonreactive CSF FTA-ABS makes neurosyphilis unlikely. The CSF FTA-ABS, particularly when combined with an elevated CSF B-cell count (elevation in CSF CD191 cells), is most useful in whom neurosyphilis is suspected, but the CSF VDRL is nonreactive.[59]

TABLE 6.2 Recommendations for Lumbar Puncture With Cerebrospinal Fluid Examination in Syphilis

Neurologic or ophthalmic signs or symptoms in any stage of syphilis:

- Evidence of active tertiary syphilis affecting other parts of the body
- Treatment failure (including failure of serum nontreponemal tests to fall appropriately) in any stage of syphilis
- HIV infection with late latent syphilis or syphilis of unknown duration
- Prior to treatment of patients with symptomatic late syphilis
- A serum RPR titer greater than or equal to 1:32 and/or the presence of HIV infection with a CD4 count less than 350 cells/mm^3

RPR, rapid plasma reagin.

Data from McGrath JW, Strasburger VC, Cushing AH. Secretory IgA in cervical mucus. *J Adolesc Health*. 1994;15(5):423–425; Ghanem KG, Moore RD, Rompalo AM, et al. Lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms. *Clin Infect Dis*. 2009;48(6):816–821; Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis*. 2004;189(3):369–376.

If CSF pleocytosis was present on the initial evaluation, a CSF examination should be done every 6 months to ascertain treatment success.[1] Changes in the CSF protein or CSF VDRL occur more slowly than normalization of cell counts. Failure of the CSF cell count to decrease in the first 6 months or lack of resolution of CSF pleocytosis after 2 years should prompt retreatment. When treatment failure is indicated in cardiovascular and gummatous syphilis, another course of benzathine penicillin is required, whereas neurosyphilis usually requires 14 days of intravenous penicillin G.[1]

Tertiary syphilis expresses gummas, which are lesions with a coagulated, necrotic center resulting in small-vessel obliterative endarteritis. Gummas may present anywhere, including the skin, bones, and visceral organs. Visceral gummas may present as a mass lesion. Gummatous syphilis is the most uncommon type of late syphilis.

Diagnosis

T. pallidum cannot be cultured in a laboratory so diagnosis must be made by direct visualization of the organism via darkfield examination, serology, or DFA testing. Darkfield examination and direct fluorescent antibody test for *Treponema pallidum* (DFA-TP) of lesion exudate or tissue sample are definitive methods for early diagnosis of syphilis. Darkfield examination is

recommended for patients with a chancre because serologic testing may be nonreactive during initial infection. Darkfield examination has a specificity of 70 to 95%, depending on the expertise of the operator; a positive examination requires the presence of at least 10 organisms in the specimen.[60] DFA-TP is specific for *T. pallidum* antigens but requires a fluorescence microscope and a trained and experienced technologist. In both of these methods, it is important to note that a negative test does not totally exclude the diagnosis of syphilis.

The diagnosis of syphilis is most commonly made using serologic-based testing. Because serologic testing depends on a humoral immune response to infection, it is an indirect method of testing. Serologic testing involves a two-step process, beginning with a nonspecific test and concluding with a treponeme-specific test (Table 6.3). Nontreponemal tests assess reactivity of patient serum to a cardiolipin-cholesterol-lecithin antigen. The nontreponemal screening tests include the VDRL, rapid plasma reagin (RPR), automated reagin test (ART), and toluidine red unheated serum test (TRUST). The sensitivities of all serologic tests are less than 90% in primary syphilis when antibody responses may still be developing.[61] The sensitivity of these tests increases with the duration of infection.

When using serologic assays to diagnose syphilis, it should be noted that IgM and immunoglobulin G (IgG) antitreponemal antibodies may respectively take 2 and 4 weeks to appear postinfection. Nontreponemal tests are semiquantitative, and antibody titers, which usually correlate with disease activity, should be reported quantitatively. A four-fold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results that were obtained using the same serologic test. Sequential serologic tests in individual patients should be performed using the same testing method, and, if possible, in the same laboratory. The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers frequently are slightly higher than VDRL titers. Treatment accelerates the pace of antibody decline although titers will naturally decline without treatment. In some people, nontreponemal antibodies can persist for a long period of time—a response referred to as the "serofast reaction."

Nonspecific tests (VDRL, RPR, ART, or TRUST) may be falsely negative early in the course of the infection before serum antibodies have developed or when a prozone phenomenon occurs. A prozone reaction occurs when high antibody titers interfere with the formation of antigen-antibody complexes during agglutination, resulting in an overabundance of nonbinding antibodies and a negative reaction. A negative nontreponemal test can occur in up to 40% of infected patients.[60] Testing should be repeated 1 to 2 weeks after a negative test result if clinical suspicion is high.

False-positive results using nontreponemal testing may occur with other disease states or physiologic conditions. Any strong immunologic stimuli, including recent vaccinations, acute viral or bacterial infections, intravenous drug use, tuberculosis, chronic liver disease (CLD), autoimmune disorders, and connective tissue diseases, may cause a false-positive reaction. False-positive tests are particularly common during pregnancy. Diseases due to other treponemes (e.g., Lyme disease) may also cause false-positive treponemal test results. Tests may be falsely positive up to 6 months due to these conditions. Approximately 1 to 2% of patients in the United States will have a false-positive nontreponemal test. Because the current incidence of syphilis is low, the majority of positive screening tests will not be due to treponemal infection.

Treponemal-specific tests are necessary to confirm the diagnosis of syphilis after a positive nontreponemal test result in order to avoid treating false positives. Treponemal-specific tests include FTA-ABS, microhemagglutination assay for antibodies to *Treponema pallidum* (MHA-TP), *Treponema pallidum* particle agglutination assay (TP-PA), and *Treponema pallidum* enzyme immunoassay (TP-EIA). These qualitative tests are specific for *T. pallidum* antigens and are reported as reactive or nonreactive. The TP-PA is more commonly used than the FTA-ABS because it is less expensive and simpler to perform. Treponemal tests are only applicable to patients with no previous history of syphilis and should not be used to assess treatment response. In the majority of patients (75 to 80%), once a specific treponemal test is positive, it stays positive for life. When both the nontreponemal and treponemal tests are reactive, a

TABLE 6.3 Interpretation of Serologic Testing for Syphilis

Definitive diagnosis: Both nontreponemal and treponemal tests are reactive.

Patients with a history of treated syphilis

- If there is a four-fold increase in titer on a nonspecific treponemal test, reinfection has occurred with the caveat that some patients may remain "serofast," that is, nontreponemal tests are still reactive but at low titer (e.g., 1:2) despite past treatment that was successful.
- Specific treponemal tests may remain positive for years and should not be used to diagnose reinfection.
- If treatment occurs early enough, the patient may serorevert to negative in both nontreponemal and treponemal serologic studies.

False-positive tests

- False positives may occur with nonspecific and specific treponemal tests.
- A reactive nontreponemal test followed by a nonreactive treponemal test is a false positive.

False-negative tests

- May occur with nonreactive nontreponemal test in a patient with strong clinical signs or symptoms of infection
- Repeat serologic testing in 1 to 2 weeks.

diagnosis of syphilis is confirmed unless prior treatment history rules out a diagnosis.

Newly acquired syphilis infection can be diagnosed in patients who were previously treated if RPR testing reveals a four-fold increase in titer. The CDC recommends that all titers be compared using the same test methodology in the same laboratory to avoid variation of test results. Reinfection can be diagnosed using the following criteria:

- Prior history of an appropriate treatment regimen
- Clinical manifestations of either primary or secondary syphilis
- History of new risk factors
- A four-fold decline in RPR titers after retreatment (If possible, all titers should be compared using the same test methodology.)

For discordant test results, the CDC has several recommendations to guide patient management.[1] For patients with no history of treatment who have a positive treponemal test and a negative nontreponemal test, a second differential treponemal test should be done. If the second treponemal test is negative, the clinician decides, based on history, if further evaluation or treatment is necessary or, alternatively, they may choose to perform a third treponemal test. If the second treponemal test is positive, clinicians should offer treatment for late latent infection and, unless history or physical examination suggests otherwise, the patients may be considered unlikely to be infectious. For patients with a history of treatment for syphilis, a negative nontreponemal test will require no further management or testing unless their sexual history suggests a risk of reexposure.

Rapid care testing for *T. pallidum* infection has not been approved by the U.S. Food and Drug Administration (FDA) for routine syphilis testing. A performance comparison of nine different rapid tests demonstrated that test sensitivity ranges from 85 to 98% and specificity ranges from 93 to 98%.[62] Although these tests are low cost and highly sensitive and specific, they cannot distinguish between active and treated syphilis.

Treatment

T. pallidum has a slow metabolism and divides slowly, averaging one doubling in vivo per day. Long-lasting penicillin G in benzathine, aqueous procaine, or aqueous crystalline form is the drug of choice for treatment of all stages of syphilis (see Table 6.4 for treatment protocols for syphilis). Because of the high rate of failure of other treatment modalities, particularly in pregnancy, it is recommended that patients with known penicillin allergy undergo desensitization with subsequent administration of penicillin.[1] An oral desensitization protocol is available in Table 6.5. Clinicians should inform patients that if antibiotic therapy is stopped for more than 24 hours, repeat desensitization is required if penicillin is to be used again. The first dose of benzathine penicillin should be given via the intramuscular route at the completion of the oral desensitization protocol.

Only the long-acting forms of benzathine penicillin should be used for syphilis treatment because it provides continuous low doses of penicillin. It is administered intramuscularly (IM) because intravenous administration has been associated with cardiopulmonary arrest and death. Bicillin L-A (2.4 million units of benzathine penicillin G) has demonstrated detectable serum concentrations for up to 30 days. In contrast, Bicillin C-R (equal concentrations of procaine and benzathine penicillin G) should not be used to treat syphilis because serum drug levels last for only 7 days. If patients treated for late or latent syphilis miss a dose, an interval of 10 to 14 days may be acceptable before the treatment regimen should be restarted.[1]

Within hours after antibiotic treatment, patients can develop an acute complication known as the Jarisch-Herxheimer reaction, which is an acute febrile reaction within the first 24 hours of treatment. Symptoms include fever, chills, myalgias, headache, tachycardia, hyperventilation, vasodilation, and mild hypotension. Although the reaction occurs in 10 to 25% of patients overall, it is most common in the treatment of secondary

TABLE 6.4 Treatment of Syphilis

	Stage of Infection			
	Primary, Secondary, or Early Latent	**Late Latent or Latent of Unknown Duration**	**Neurosyphilis**	**Special Considerations**
Preferred treatment regimen	Benzathine penicillin G 2.4 million units IM (one dose)	Benzathine penicillin G 7.2 million units total, given as three doses of 2.4 million units IM each at 1 wk intervals	Aqueous crystalline penicillin G 18–24 million units per day, given as 3–4 million units IV every 4 h or as a continuous infusion for 10–14 d	
Alternative treatment regimen	Doxycycline 100 mg orally twice daily for 14 d or tetracycline 500 mg orally four times a day for 14 d	Doxycycline 100 mg orally twice daily for 14 d or tetracycline 500 mg orally four times a day for 14 d	Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg orally four times a day, both for 10–14 d	Pregnant women must be desensitized and given penicillin regimens.

From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010.* Atlanta, GA: U.S. Department of Health and Human Services; 2011.

TABLE 6.5 Oral Penicillin Desensitization Protocol

Dose[a]	Amount[b] Penicillin V Suspension (U/mL)	(mL)	(U)	Cumulative Dose (U)
1	1000	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1500
5	1000	1.6	1600	3100
6	1000	3.2	3200	6300
7	1000	6.4	6400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,700	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,000
12	80,000	2.4	164,000	336,700
13	80,000	4.8	320,000	656,700
14	80,000	8.0	640,000	1,296,700

[a] Interval between doses: 15 minutes; elapsed time: 3 hours and 45 minutes; cumulative dose: 1.3 million units.
[b] The specific amount of drug is diluted in approximately 30 mL of water and then given orally.
Patients will be desensitized as above. After desensitization, patients will be observed for 30 minutes before parenteral injection of benzathine penicillin.
Patients who have been desensitized previously, who have received their benzathine penicillin IM, and who are returning for their second shot will not require additional desensitization. Although desensitization is usually lost within 2 days of terminating the penicillin therapy, long-acting benzathine penicillin will sustain the sensitized state for periods up to 3 weeks.
Adapted from Hutto C, Arvin A, Jacobs R, et al. Intrauterine herpes simplex virus infections. *J Pediatr.* 1987;110:97–101.

syphilis. Symptoms last for 12 to 24 hours and are usually self-limiting. Patients can be treated symptomatically with antipyretics. All patients receiving initial treatment should be counseled regarding this reaction and instructed to report any symptoms they may develop.

For nonpregnant patients who are allergic to penicillin and who refuse penicillin desensitization or if it is not available, other treatment options include doxycycline, tetracycline, macrolide, and ceftriaxone regimens, although data regarding their effectiveness are limited. Azithromycin should be used with caution because *T. pallidum* chromosomal mutations have been associated with azithromycin resistance and treatment failures have been documented.

Response to therapy should be monitored with clinical and serologic examination at 3, 6, and 12 months.[1] The level of antibody decline depends on the stage of infection and the antibody titer before treatment. Early syphilis may result in a faster antibody decline than latent syphilis. Clinical significance is indicated with a four-fold change in titer (e.g., from 1:16 to 1:4). A repeat titer should be obtained before initiation of treatment because titers can increase dramatically over a few days. Failure of nontreponemal antibody titers to decrease four-fold at 6 months indicates probable treatment failure or possible reinfection in primary or secondary syphilis. These patients should also be tested for HIV. However, in patients with high titers pretreatment (greater than 1:32), an observed decline may take 12 to 24 months, so as long as the titer is not rising, follow-up should be conservative. For patients with latent syphilis, an additional antibody titer should be performed at 24 months posttreatment. Titers should decline at least four-fold by 12 to 24 months after treatment. However, 15% of patients do not meet criterion for serologic cure 12 months after appropriate treatment and may remain "serofast." A serofast state occurs when a patient's nontreponemal titers persist at low levels (e.g., 1:2) even with appropriate therapy. The mechanism for this phenomenon is unknown. Periodic rechecking of titers in serofast patients is recommended. If follow-up cannot be ensured, retreatment and consideration of CSF examination may be considered. Additionally, all serofast patients should be tested for HIV infection as a potential cause of antibody deficiency. A four-fold rise in the antibody titer (e.g., 1:4 to 1:16) would indicate reinfection and retreatment with benzathine penicillin (2.4 million units IM weekly for 3 weeks) is recommended.

Sexual partners should also be evaluated and treated for infection according to recommendations by the CDC.[1] Presumptive treatment is recommended for sexual partners who were exposed within 90 days preceding a diagnosis even if they are seronegative or if they are exposed after 90 days and no serologic testing or follow-up is available. For purposes of partner notification and presumptive treatment, the CDC recommends that patients with an unknown duration of syphilis who have high nontreponemal titers (e.g., greater than 1:32) can be assumed to have early syphilis. For long-term partners of patients with latent syphilis, clinical and serologic evaluations of the partner(s) should be done to guide treatment.

Cardiovascular syphilis can be treated with benzathine penicillin G 2.4 million units IM once weekly for 3 weeks. Although therapy does not reverse the cardiovascular complications associated with syphilis, it may delay disease progression. Recommended doses of benzathine penicillin are not detectable in CSF; therefore, intravenous penicillin G is recommended for the treatment of neurosyphilis. Intravenous penicillin G (3 to 4 million units IV every 4 hours or 18 to 24 million units every 24 hours by continuous infusion for 10 to 14 days) should be administered to the following:

- Patients with syphilitic uveitis or other ocular manifestations of syphilis
- Patients with auditory disease secondary to syphilis
- Patients strongly suspected of having late CNS syphilis (e.g., compatible clinical syndrome, positive blood serology, and CSF pleocytosis with a nonreactive CSF VDRL. In HIV-infected patients, an RPR or VDRL

titer of greater than1:32 and a CD4 count of less than 350 cells/mm^3 is strongly suggestive of CNS syphilis).[63]

If compliance can be ensured, procaine penicillin (2.4 million units IM once daily) plus probenecid (500 mg orally four times a day) for 10 to 14 days is an outpatient option recommended by the CDC.[1] It should be noted that probenecid is contraindicated in patients with sulfonamide allergy. Although this combination provides higher serum levels than benzathine penicillin, CSF levels are often not detectable, and this regimen has not been well studied for the treatment of neurosyphilis. The duration of treatment for neurosyphilis (10 to 14 days) is shorter than the treatment for late syphilis in the absence of neurosyphilis, which is 3 weeks. Therefore, the CDC suggests that a benzathine penicillin regimen can be considered after completion of a treatment regimen for neurosyphilis in order to achieve a comparable duration of therapy. Although data is limited, an alternative treatment for patients who have a mild penicillin allergy is ceftriaxone (2 g IV daily) for 10 to 14 days, with careful observation for allergic responses to ceftriaxone.[64]

In cases of neurosyphilis, if CSF pleocytosis was present originally, CSF samples should be examined every 6 months for follow-up until the cell count is normal. If there is no decrease in cell count by 6 months or it has not returned to normal within 2 years, retreatment should be considered.

Special Considerations

Syphilis in Pregnancy

Testing during pregnancy is recommended at the first prenatal visit, and again in the third trimester, particularly in high-risk populations. In the United States, state laws may mandate serologic screening at delivery. The only effective treatment for the prevention of congenital syphilis in pregnancy is penicillin G. Treatment of syphilis during pregnancy should adhere to the penicillin regimen as recommended for the specific stage of syphilis. Some experts recommend administering a second injection of benzathine penicillin G 2.4 million units IM 1 week after the first to treat primary, secondary, or early latent syphilis in pregnancy.[65] During pregnancy, alternative therapies for penicillin-allergic women are NOT acceptable because they are either ineffective (erythromycin), contraindicated (tetracycline), lack efficacy data (ceftriaxone), or are associated with treatment failure (azithromycin). The only treatment recommended for penicillin-allergic pregnant patients with syphilis is desensitization followed by penicillin therapy. If a woman is treated during the second half of pregnancy and treatment precipitates the Jarisch-Herxheimer reaction, she may also experience preterm labor and/or fetal distress. This risk does not preclude the need for treatment. Syphilis diagnosed during the second half of pregnancy should prompt a sonographic evaluation for congenital syphilis, although this evaluation should not delay treatment of the mother.

Following treatment, titers should be repeated at 28 to 32 weeks' gestation and at delivery as recommended for the disease stage. Women with a high risk of reinfection or in areas with a high prevalence of syphilis should be tested monthly. The decline in titer during pregnancy is similar to nonpregnant patients so a four-fold decrease should be seen by 6 months posttherapy, and the test should become nonreactive by 12 to 24 months. Treatment is likely to be inadequate if delivery occurs within 30 days of therapy, if there are clinical signs of infection at delivery, or if the titer at delivery is four-fold higher than it was prior to treatment. Symptomatic fetal infection before 20 weeks of gestation is rare; therefore, treatment during the first 20 weeks of pregnancy almost always ensures the newborn will not be infected. Transmission with fetal neonatal infection occurs in 50 to 67% of cases with maternal primary or secondary syphilis.[66] The risk of congenital infection for early latent infection is 40 to 80% and 6 to 14% for late latent infection.[66]

Syphilis and HIV

Given the strong association between HIV and genital ulcer disease, concurrent infection with HIV and syphilis is common. A further discussion of syphilis in HIV-positive patients is found in Chapter 27.

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by *C. trachomatis* serotypes L1, L2, and L3. *C. trachomatis* is a small, Gram-negative obligate intracellular parasite. After gaining entrance through the skin or mucosa, *C. trachomatis* travels down the lymphatic channels to multiply within mononuclear phagocytes in the lymph nodes. LGV is more common in Central and South America than in North America. Before 2003, it was considered rare in more developed countries. However, a recent outbreak in the Netherlands in gay men has led to an increase of LGV throughout Europe and the United States.[67] A majority of these patients are coinfected with HIV.[68,69]

Clinical Symptoms

LGV is a disease of the lymphatic tissues primarily and induces a lymphoproliferative response. This is different from mucosal chlamydial infections where the reaction largely remains at the site of infection. Overall, LGV is six times more common in men than women.[70] LGV may be transmitted through any type of unprotected intercourse regardless if it is oral, vaginal, or anal. Other possible modes of transmission of the pathogen include sharing of sex toys as well as sexual behaviors such as fisting. The incubation period of LGV is variable, ranging from 4 to 21 days. Asymptomatic female carriers are known to exist.

The primary lesion of LGV may be a papule, an ulcer or erosion, a small herpetiform lesion, or nonspecific urethritis. In women, the primary lesion is usually located on the posterior aspect of the vagina or cervix, or on the vulva. The lesion heals within a few days. Approximately 1 to 4 weeks later, the secondary stage begins as indicated by tenderness and swelling of the lymph nodes that drain the primary lesion, usually the inguinal and femoral nodes. When femoral nodes are involved, the inguinal ligament may produce a "groove" sign; in rare cases, this may be bilateral. The iliac or obturator nodes can also be involved, depending on the location of the primary lesion. About 20 to 30% of women have the characteristic inguinal involvement. The lymphadenopathy, also called buboes, may progress to extensive adenitis that can rupture through multiple draining sinuses. Genital and colorectal lesions of LGV may be secondarily infected with bacteria or coinfected with other STIs or non–sexually transmitted organisms. Left untreated, or if it is undertreated, the infection continues with tissue destruction, fibrosis, and scarring. As a result, sinuses, fistulas, and strictures involving the vulva, perineum, and rectum may develop. With inadequate treatment or no treatment, end-stage complications such as genital elephantiasis, anal fistulas or strictures, frozen pelvis, and infertility may be seen.

Women who engage in rectal intercourse may develop LGV proctocolitis characterized by rectal bleeding or discharge, pain, fever, tenesmus, and constipation. These symptoms may be misdiagnosed as inflammatory bowel disease. Complications may include chronic colorectal strictures or fistulas.

Diagnosis

Diagnosis of LGV may be difficult, particularly because of the rarity of the condition. LGV diagnosis is based on clinical suspicion, epidemiologic information, and the exclusion of other etiologies for proctocolitis, inguinal lymphadenopathy, or genital or rectal ulcers. Swabs from the primary lesion or from lymph node aspirates may be tested for *C. trachomatis* by culture, direct immunofluorescence, or nucleic acid detection. It should be noted that the yield from ulcers or node aspirations by culture is low, about 30% overall, and in many areas, *Chlamydia* culture is only available in large referral centers.[71]

Nucleic acid amplification technique/testing (NAAT) are not FDA approved for testing rectal specimens. Positive chlamydial serology for acute infection using either microimmunofluorescence (MIF) or complement fixation (CF) may support the diagnosis of LGV, although they do not identify specific serotypes. A four-fold rise in titer upon CF testing or a single titer of 1:64 or higher indicates active infection, whereas a titer of less than 1:32 generally excludes LGV infection.[1,71] Serial titers demonstrating a titer rise are confirmatory. Diagnosis can also be made by isolating *Chlamydia* from infected tissue and occasionally on histopathology. Culture of purulent aspirate from buboes may yield the best results, but isolation rates are low—30% in the second stage of infection.[71] PCR techniques can also be used to identify the organism and differentiate between LGV and non-LGV *C. trachomatis* but these tests are not widely available.[72]

All patients diagnosed with LGV should be tested for HIV infection and other STDs, including hepatitis B and C.

Treatment

Treatment is aimed at curing symptoms and infection and preventing further tissue damage, although scarring may still occur. Buboes may require drainage through incision or needle aspiration in order to avoid rupture, sinus formation, or formation of inguinal/femoral ulcerations. The recommended treatment for LGV and other STIs may be found in Table 6.6. Refer to Table 6.7 for recommendations on the treatment of partners for those infected with LGV and other STIs. Pregnant and lactating women should be treated with erythromycin because there is no data on the efficacy of azithromycin during pregnancy and doxycycline is contraindicated.

Suspected LGV proctocolitis should be treated with 100 mg orally twice daily for 7 days in conjunction with a one-time dose of 125 mg ceftriaxone IM. If LGV proctocolitis is confirmed, the doxycycline should be given for 21 days or for the duration of symptoms.[68]

Sexual contacts within 60 days of the onset of the patient's symptoms should be examined, tested for urethral or cervical chlamydial infection, and treated with a chlamydia regimen (azithromycin 1 g orally single dose or doxycycline 100 mg orally twice a day for 7 days).

Persons with both LGV and HIV infection should receive the same regimens as those who are HIV negative although treatment may need to be prolonged.

Chancroid

Chancroid is a genital ulcer disease caused by *H. ducreyi*, a small, fastidious Gram-negative coccobacillus. It is very rare in the United States where only 24 cases were reported in 2009.[73] *H. ducreyi* is strictly a human pathogen, with no known animal or environmental reservoirs. Although it is uncommon, chancroid is highly contagious. Only a few organisms are required for infection, and transmission occurs in approximately 70% of sexual exposures.[74] Coinfection with *T. pallidum* and/or herpes is common. Chancroid is a public health problem because *H. ducreyi* and HIV facilitate each other's transmission.[75]

Clinical Symptoms

The incubation period is 4 to 10 days, although it may range from 1 to 35 days. Lesions usually begin as small papules which progress to pustules and then erode over 1 to 3 days to relatively painful ulcers. Ulcers range in size from 1/8 to 2 inches in diameter and are deep with ragged borders and a purulent, yellow-gray base that bleeds easily when it is scraped. Most infected persons

TABLE 6.6 Treatment Regimens for Sexually Transmitted Infections

Human Papillomavirus	
Medical Options	**Surgical Options**
Condylox 0.5% Imiquimod 5% Bi- or trichloroacetic acid up to 85% Podophyllin 10% solution	Cryotherapy LEEP excision CO_2 laser ablation
Molluscum Contagiosum	
Options	
Imiquimod Podophyllin Cryotherapy Trichloroacetic acid Skin curettage	
Lymphogranuloma Venereum	
Recommended	**Alternative**
Doxycycline	Erythromycin Azithromycin
Chancroid	
Recommended	**Comments**
Azithromycin Ceftriaxone Ciprofloxacin Erythromycin	Drain buboes. Do not excise nodes.
Chlamydia	
Recommended	
Azithromycin 1 g Doxycycline 7 days	
Gonorrhea	
Recommended	**Concurrent**
Ceftriaxone 250 mg IM in a single dose OR, IF NOT AN OPTION: Cefixime 400 mg orally in a single dose OR Single-dose injectable cephalosporin regimens	See regimen for chlamydia.
Granuloma Inguinale	
Options	**Alternative**
Doxycycline 21 days	Azithromycin Ciprofloxacin Erythromycin or trimethoprim-sulfamethoxazole
Scabies	
Recommended	**Alternative** / **Infants**
Permethrin cream 5% Ivermectin	Lindane 1% / Pyrethrins/piperonyl butoxide
Pediculosis	
Permethrin 1% Malathion 0.5% Ivermectin	
Trichomoniasis	
Metronidazole 2 g once Tinidazole 2 g once	

LEEP, loop electrosurgical excision procedure.
From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010.* Atlanta, GA: U.S. Department of Health and Human Services; 2011.

have more than one ulcer, and the lesions are confined to the genitals and the lymph nodes that drain the genitals. In women, most of the lesions are located at the entrance to the vagina, but some infected women may have internal vaginal and cervical ulcers that are painless. Left untreated, ulcers may persist for 1 to 3 months. Although *H. ducreyi* does not disseminate systemically, extragenital lesions do occur and are thought to be due to autoinoculation. Data from outbreaks of chancroid show that infection does not impart lifelong immunity, and patients who have had chancroid may have repeated infections.[76]

Inguinal lymphadenitis is present in less than 50% of infected women.[77] Approximately 25% of cases may develop fluctuant buboes 7 to 10 days after the appearance of the lesion. Fluctuant lymphadenitis may be treated with either fine needle aspiration or incision and drainage. Left untreated, the buboes can enlarge and may drain spontaneously or require drainage for resolution of symptoms.

Diagnosis

A clinical diagnosis may be difficult because chancroid is uncommon in the United States. Clinicians may not include this infection in their differential diagnosis, which may lead to inappropriate empiric therapy. A definitive diagnosis of chancroid requires the identification of *H. ducreyi* from genital ulcers or infected inguinal nodes. The most reliable material to use for culture is purulent material aspirated from a bubo. Special culture media are required but are not widely available, and even when proper media are used, the sensitivity of culture is less than 80%. A specimen can be collected by cleansing the area with sterile physiologic saline followed by swabbing the base of the genital ulcer using a calcium alginate, Dacron, or cotton swab. Identification of *H. ducreyi* can also be made using a Gram stain to reveal a "railroad track" or "school of fish" pattern, although the sensitivity of the Gram stain is poor. Although there are currently no FDA-approved commercially available PCR tests for chancroid, the multiplex polymerase chain reaction (M-PCR) used alone or combined with enzyme immunoassay (EIA) has been employed in research settings and is more sensitive than culture.

Because a definitive diagnosis requires isolation of *H. ducreyi* from a lesion and there are no available diagnostic tests that are rapid and reliable, most cases are treated empirically. The CDC notes that a probable diagnosis for both clinical and surveillance purposes can be made if all of the following criteria are met: (a) the patient has one or more painful genital ulcers; (b) there is a negative darkfield microscopic examination for *T. pallidum*, negative serologic test for syphilis performed at least 7 days after onset of ulcers; (c) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; and (d) HSV culture is negative.[1]

TABLE 6.7 Sexually Transmitted Diseases: Should the Partner(s) Be Treated?

		Treat Partners?		
	Average Incubation	Yes	No	Which Partners?
Herpes	3–7 d		X	
Venereal warts	3–6 mo		X	
Molluscum contagiosum	2–7 wk	X		Partners in last 1–2 mo; examine and treat if affected
Lymphogranuloma venereum	4–21 d	X		Last 30 d
Chancroid	5–7 d	X		Immediate
Chlamydia	1 d–several weeks	X		Last 1–2 mo
Gonorrhea	3–5 d	X		Immediate
Syphilis	10–90 d (primary)	X		All contacts in primary, secondary, and early latent; late latent and tertiary not sexually communicable
Granuloma inguinale	1–360 d		X	
Pediculosis	30 d	X		Contacts in last month
Scabies	4–6 wk	X		Contacts in last 4–6 wk

Treatment

The goal of treatment is to prevent transmission, resolve symptoms, and cure infection. See Tables 6.6 and 6.7. Patients should be seen for follow-up within 7 days after initiation of treatment—most patients should begin to improve within 3 days. If there is no clinical improvement within 3 to 7 days, consideration must be given to the following possibilities: (a) the diagnosis is incorrect, (b) there is coinfection with another STI, (c) the patient has HIV, (d) treatment was not taken appropriately, and (e) the *H. ducreyi* strain causing the infection is resistant to the prescribed antimicrobial. Time to complete resolution depends on the size of the ulcers and may take up to 2 weeks. Resolution of fluctuant lymphadenopathy is slower than for ulcers and may require aspiration or incision and drainage through adjacent healthy skin. Incision and drainage might be preferred because of reduced need for subsequent drainage procedures.

Because coinfection is known to occur, patients with chancroid should also be tested for HIV and tested and empirically treated for syphilis.[1] Additionally, patients should be retested for syphilis and HIV 3 months after the diagnosis of chancroid if the initial test results are negative. Sex partners should also be examined and treated if they have had sexual contact with the patient within 10 days of symptom presentation, regardless of symptomatology, and the couple should abstain from any sexual contact until the treatment is completed.

Granuloma Inguinale (Donovanosis)

Granuloma inguinale, or donovanosis, is a genital ulcer disease caused by *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*), a Gram-negative coccobacilli. There are fewer than 100 cases per year in the United States, but it is more frequent worldwide. In studies with human volunteers, the average incubation time is 50 days.[78] Donovanosis increases the risk of HIV acquisition.

Clinical Symptoms

The initial lesion consists of a small, painless papule or nodule that soon ruptures and leads to the formation of an ulcer that grows slowly, bleeds easily, and is painless. Over time, the ulcers are well-defined, granulomatous lesions with a circular or snakelike appearance. The ulcers are commonly located in the folds of the skin and can become extensive. Frequently, they are secondarily infected and may emit a rank odor. Over time, the disease may be locally confined or extended or disseminate hematogenously. Subcutaneous granulomas (pseudobuboes) might also occur. Inguinal adenopathy is not present in either the localized, extensive, or disseminated versions of the disease.

In women, the most common sites involved are the labia and fourchette and, less frequently, the vaginal walls. It may also appear as a cervical lesion, which occasionally mimics a cervical cancer and may extend to the pelvis. The lesions are highly vascular, have a beefy red appearance, and bleed easily on contact. Inguinal groin swellings, or pseudobuboes, result from the subcutaneous spread of granulomas into the inguinal region without actual adenitis. Lymphedema and subsequent elephantiasis due to fibrotic destruction of the draining lymph systems of the external genitalia may result. This is the most common complication of donovanosis and occurs more frequently in women than in men.

Donovanosis can disseminate to intra-abdominal organs such as the abdominal cavity, intestines, spleen, liver, lungs, uterus, and ovaries. Dissemination occurs more frequently in areas where the disease is endemic. Systemic disease is more common in women, particularly those with primary lesions of the cervix.

Granuloma inguinale has a more aggressive course during pregnancy and should be suspected in women with atypical genital lesions attending antenatal clinics. Cases in children are frequently associated with contact with infected adults, although not necessarily because of sexual abuse.[78]

Diagnosis

Diagnosis is usually made on clinical grounds and can be confirmed with direct visualization of Donovan bodies in ulcer smears obtained by punch biopsy or by a biopsy performed on the ulcer. *K. granulomatis* cannot be routinely cultured using conventional media. No serologic tests are currently used for diagnosing granuloma inguinale.

Treatment

Healing typically proceeds inward from the ulcer margins and prolonged therapy is required to permit granulation and re-epithelization of the ulcers. Treatment should be continued for at least 6 weeks or until all lesions have completely healed (see Tables 6.6 and 6.7).[79] The addition of gentamicin 1 mg/kg IV every 8 hours to these regimens should be considered if lesions do not respond within the first few days of therapy. Patients should be followed until symptoms are resolved. Relapse can occur 6 to 18 months after therapy that appeared effective has been discontinued.

Pregnant and lactating women should be treated with the erythromycin regimen, and consideration should be given to the addition of a parenteral aminoglycoside (e.g., gentamicin). Persons with both donovanosis and HIV infection should receive the same regimens as those who are HIV negative; consideration should be given to adding a parenteral aminoglycoside (e.g., gentamicin) to the therapeutic regimen. Apart from antibiotic treatment, surgical intervention is often necessary in order to correct some side effects of the disease.

Diseases Characterized by Cervicitis

Cervicitis is characterized by purulent or mucopurulent endocervical exudate (mucopurulent cervicitis) and/or sustained endocervical bleeding induced by gentle swabbing. Some women may also complain of dyspareunia, dysuria (usually due to concurrent urethral infection), or vulvovaginal irritation. Cervicitis may be due to infectious or noninfectious causes, and it may be symptomatic or asymptomatic. Although the inflammation of the cervix proper is frequently asymptomatic, patients may complain of an abnormal vaginal discharge and intermenstrual vaginal bleeding (e.g., after sexual intercourse). Although cervical infections due to *C. trachomatis* or *N. gonorrhoeae* are the most common causes of cervicitis, only a small proportion of women with these infections develop cervicitis. Herpes simplex and trichomoniasis infections may present as cervicitis. Limited data indicate that infection with *Mycoplasma genitalium* and bacterial vaginosis (BV) and frequent douching might cause cervicitis.[80–83] Because cervicitis is frequently a sign of upper genital tract infection, patients with signs of cervicitis should also be assessed for symptoms of PID. Cervicitis is associated with a significant increase in risk of HIV-1 acquisition and shedding.[84] Noninfectious etiologies may include douching, chemical irritation (perhaps latex), local contraceptive devices, and systemic diseases, for example, Behçet disease. In most cases of cervicitis, no causative organism is identified.

Women seeking care for cervicitis should be tested for *C. trachomatis* and for *N. gonorrhoeae* using nucleic acid amplification technique/testing (NAAT) on either vaginal, cervical, or urine samples. These women should be evaluated for BV and trichomoniasis as well and treated accordingly. Women with symptomatic cervicitis and negative microscopy for trichomonads should receive further testing (i.e., culture or other FDA-cleared method) because the sensitivity of microscopy is low (about 50%). Standardized diagnostic tests for *M. genitalium* are not commercially available, and routinely testing for infections other than *Trichomonas vaginalis*, gonorrhea, chlamydia, and BV is not useful unless a specific organism, such as HSV, is suspected.

The appearance of the cervix will vary, depending on the severity of the inflammation/infection and the etiology. Mucopurulent discharge with edema and easy friability are characteristic of chlamydial and gonococcal infections, especially in women younger than age 25 years.[85] Diffuse vesicular lesions or ulceration is suggestive of HSV, whereas a "strawberry cervix" of punctuate hemorrhages (colpitis macularis) is suggestive of *T. vaginalis* infection. However, it is not generally possible to distinguish infectious from noninfectious acute cervicitis by physical examination so further diagnostic testing is indicated.

Patients with clinical symptoms or signs of cervicitis should be treated empirically at the time of examination in women at increased risk for the common STIs (e.g., women younger than age 25 years, those with new or multiple partners, or who have unprotected sex), in instances where follow-up is uncertain, and in situations where a relatively insensitive diagnostic test is used in place of NAAT.[1] Inflammation on cervical cytology or biopsy are not indications for treatment. An empiric treatment regimen for cervicitis should include coverage of CT, especially in women younger than 25 years of age. Empiric therapy for gonorrhea should be included if the patient's individual risk is high or the local prevalence is high (greater than 5%).[86] The CDC recommendations for empiric therapy include azithromycin 1 g orally as a single dose OR doxycycline 100 mg orally twice a day for 7 days. Treatment of cervicitis in HIV-infected women is the same for HIV-negative women. Treatment,

follow-up, and management of sex partners depend on the results of the diagnostic tests. Patients should abstain from sex during treatment.

In cases of persistent cervicitis where relapse and/or reinfection with a specific STI has been excluded, BV is not present, and sex partners have been evaluated and treated, management options for persistent cervicitis are not well-defined. The use of repeated or prolonged administration of antibiotic therapy for persistent symptomatic cervicitis is unknown. If repeat testing for gonorrhea and chlamydia is negative, as are all other further diagnostic tests for BV or trichomoniasis, and partners have been appropriately treated and there is no evidence of exposure and all other iatrogenic causes (e.g., douching), consideration may be given to empirically trying a single, 1-g dose of azithromycin to treat *M. genitalium* infection if this has not been done already. *M. genitalium* is very difficult to culture, and there are no commercially available PCR or transcription-mediated amplification (TMA) tests available; azithromycin appears to be superior in treating it than doxycycline.[86,87]

Chlamydia trachomatis

C. trachomatis is a Gram-negative bacterium that infects the urogenital tract, commonly the cervix and/or urethra. It is an obligate intracellular parasite with a long growth cycle and two major phases to its life cycle. Within 6 to 8 hours postinfection, *C. trachomatis* produces small elementary bodies, which attach and penetrate epithelial cells, where they change into reticulate bodies and then reorganize into small elementary bodies. Within 2 to 3 days, the cell ruptures, releasing the newly formed elementary bodies and initiating the replicative process (Fig. 6.1). Because the growth cycle is long, treatment needs to be prolonged. The incubation period ranges from 7 to 14 days.

Chlamydial genital infection is the most common infectious disease reported in the United States with approximately one million new cases per year.[1] Asymptomatic infection is common among men and women (50 to 88%), thus there is a large reservoir for infection, and 46% of infections clear spontaneously within a year.[88,89] Unrecognized and recurrent infections contribute to the high prevalence and ongoing transmission rates. The prevalence is highest in patients younger than 25 years of age due to behavioral characteristics and physiologic factors. Exposure of cervical columnar epithelium may enhance susceptibility to infection.[90] Recurrent infection or persistent infection is common because infection with *C. trachomatis* induces partial immunity at best.

Clinical Symptoms

Although chlamydial infections may be asymptomatic, the clinical presentation may also range from cervicitis to PID, and long-term complications may occur.

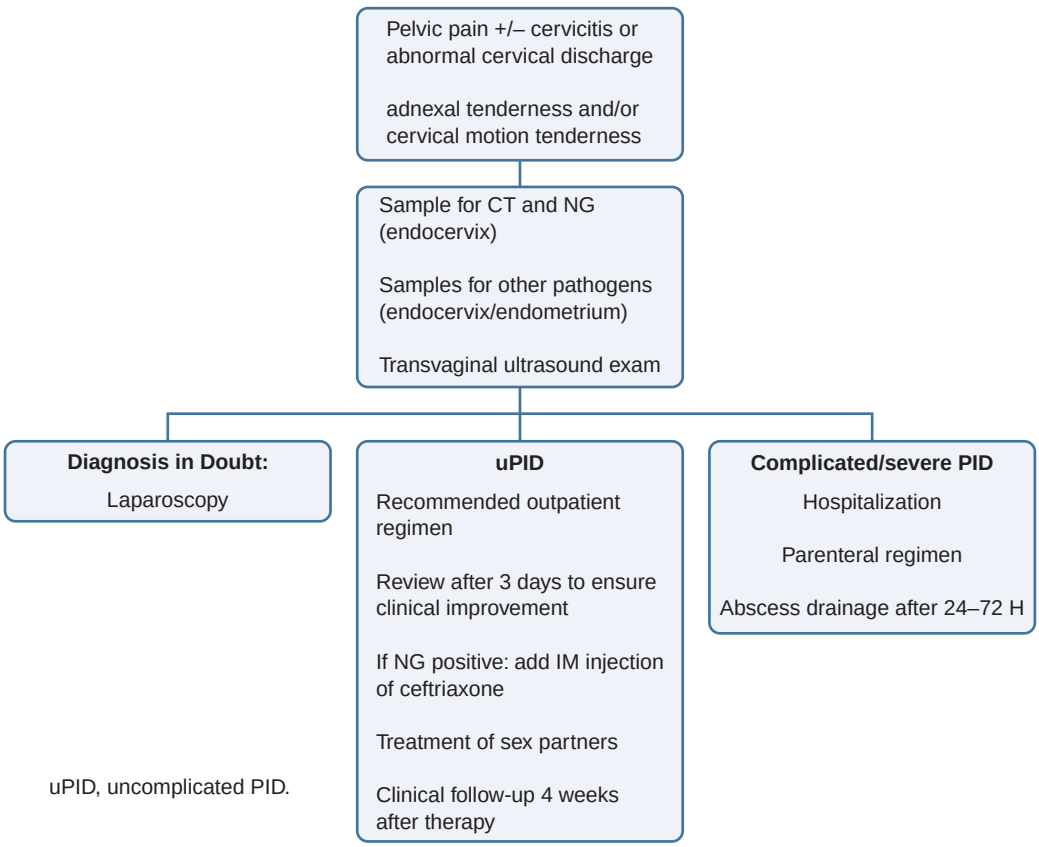

FIGURE 6.1 Management of pelvic inflammatory disease.

Chlamydial infection of the female urethra often accompanies cervicitis. Women with urethral infection complain of typical symptoms of a urinary tract infection (UTI) such as frequency and dysuria, and occasionally, lower abdominal pain. Urinalysis reveals pyuria, but no organisms are seen on Gram stain or in traditional culture.

Approximately 10 to 15% of women with untreated chlamydia infection will develop clinical PID.[91,92] Once clinical PID occurs, up to 10 to 15% of cases might lead to tubal factor infertility.[91] Chlamydia also can lead to tubal infection that is not diagnosed as PID; thus, an even greater proportion of untreated infections likely lead to infertility. Chlamydia is the leading preventable cause of tubal factor infertility.[93]

Because chlamydia and gonococcal infections coexist in a significant percentage of patients, any patient with a chlamydial urogenital infection should also be screened for gonorrhea, as well as other STIs such as syphilis and HIV.[94]

Diagnosis

Diagnosis of *C. trachomatis* infection is done using NAATs, antigen detection kits, and genetic probes. Use of cultures is now limited (often to forensic testing) and neither cytology nor serology is recommended. NAATs can be performed on a variety of samples collected noninvasively. The four NAATs currently commercially available are PCR, ligase chain reaction (LGR), strand displacement amplification (SDA), and TMA. PCR, LGR, and SDA amplify DNA, whereas TMA amplifies RNA. Antigen detection kits and genetic probe kits require urethral or cervical samples. The sensitivity and specificity for NAATs using PCR, SDA, and TMA range from 83 to 90% and 99 to 99.5%, respectively.[95]

It is important that optimal levels of nucleic acid are included in the specimen to ensure high test sensitivity. For collection of urine specimens, the patient should not cleanse her perineum in order to avoid washing off nucleic acid discharged from the cervix into the perineum. The specimen should be collected in the first part of the urine stream instead of midstream to collect the highest amount of nucleic acid. Instructions for each NAAT will specify the proper amount of urine to collect because high amounts will reduce test sensitivity. Testing in patients for both UTI and STI can present an issue if the clinician chooses a urine-based NAAT to test for STIs because cleansing of the perineum and midstream collection are considered standard procedure for UTI testing.

Treatment

See Tables 6.6 and 6.7 for recommended treatment regimens for chlamydia cervicitis and partners of those diagnosed with chlamydia. Alternative regimens recommended by the CDC include erythromycin base 500 mg orally four times a day for 7 days. Coinfection with *C. trachomatis* frequently occurs among patients who have gonococcal infection; therefore, presumptive treatment of such patients for chlamydia is appropriate.

Recent data have confirmed that azithromycin as a 1-g single dose is a safe and effective therapy in pregnant patients and in some nonpregnant patients and are preferred to a 7-day course of erythromycin base or amoxicillin.[1,96] Women who are HIV positive with chlamydia are treated the same as women who are not infected with HIV.

Except for pregnant women, retesting is not recommended after completions of treatment unless patients exhibit poor treatment compliance, remain symptomatic, or reinfection is suspected.[1] The validity of repeat testing at less than 3 weeks after completion of therapy (to identify patients who did not respond to therapy) has not been established, and if NAAT is used sooner than 3 weeks after completed treatment, a false-positive test result may result from the continued presence of nonviable organisms.

Cure rates of chlamydia for pregnant women are generally lower than in nonpregnant women, particularly when amoxicillin is used for treatment. Test of cure is recommended for all pregnant women, women with persistent symptoms, or when regimens with inferior cure rates (e.g., erythromycin or amoxicillin) have been used and should be performed no earlier than 3 weeks after treatment is initiated.

A high prevalence of chlamydia is seen in women who have been treated for it in the preceding months.[97] Most reinfections occur in women whose partners did not receive treatment or who have initiated sex with newly infected partners. Repeat infections confer an elevated risk for PID. Unlike the test of cure, which is not recommended, recently infected women are a major priority for repeat testing for *C. trachomatis*. Repeat testing is recommended at 3 months after treatment, regardless of whether the patients believe their partners were treated or not. If retesting at 3 months is not possible, it should be done whenever they next present for medical care in the 12 months following their initial therapy.

To minimize further transmission and reinfection, patients should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen. Patients should also abstain from sexual intercourse until all their sex partners have been treated. Sexual partners should be referred for evaluation, testing, and treatment.

Evidence is insufficient to recommend routine chlamydia screening for all males because of several factors, including feasibility, impact, and cost-effectiveness.[98] Screening of males is recommended in areas with high chlamydia prevalences such as adolescent clinics, correctional facilities, and STI clinics.

Scenarios where partners were asked to notify their partners of the need for medical evaluation and treatment have not been successful from a public health perspective. Expedited partner therapy (EPT), in which

presumptive medication is provided to partners in lieu of physical examination, is endorsed by the CDC as a safe and effective partner management tool.[1,19] It should be noted that EPT is not legal in all states.

Neisseria gonorrhoeae

Despite a significant decrease since 1978, *N. gonorrhoeae* infection is still the second most commonly reported STI in the United States and is a reportable STI in all states and the District of Columbia. An estimated 300,000 new cases of gonorrhea occurred in the United States in 2010.[1] Male-to-female transmission of *N. gonorrhoeae* is four-fold more likely than female to male with a risk of transmission from male to female after only one exposure of approximately 70%.[99] Fellatio carries a higher risk for acquisition of *N. gonorrhoeae* than cunnilingus.

Gonorrhea has an important epidemiologic relationship with HIV because *N. gonorrhoeae* infection often signifies risk-taking behavior, and studies show that infection with *N. gonorrhoeae* facilitates both the transmission and acquisition of HIV.[100]

Clinical Symptoms

Gonorrhea in women can involve any portion of the genital tract, the oropharynx, or become disseminated. The incubation period after exposure is 3 to 5 days; the most common site of *N. gonorrhoeae* infection in women is the cervix. Approximately 50% of women with cervical gonorrhea are asymptomatic, compared to only 10% of men who are asymptomatic.[101] Symptomatic women usually present with cervicitis with mucopurulent discharge and/or abnormal vaginal bleeding. On exam, the cervix may appear normal, have a frank discharge, or be very friable.

In addition to cervicitis, infection may also involve the urethra, Skene's glands, Bartholin's glands, anus, and pharynx. Women with gonococcal urethritis may present with complaints of dysuria. Symptoms in women may not be evident until complications, for example, PID, ectopic pregnancy, chronic pelvic pain, or infertility, are present.

Anorectal infection and proctitis due to gonorrhea may be asymptomatic, or the patient may complain of symptoms of proctitis. Up to 50% of women exposed to *N. gonorrhoeae* may have anorectal involvement. It is not certain if this results from contact with penile secretions or autoinoculation from vaginal secretions.

Oropharyngeal infection often represents asymptomatic colonization, although symptoms may occur. Although the prevalence of pharyngeal gonorrhea is estimated at 2 to 6%, if GC is found at another site, the incidence increases to 5 to 20%. Pregnant women with *N. gonorrhoeae* infection at one site have an increased risk for concurrent gonococcal infection of the oropharynx. It is important to note that nonpathogenic *Neisseria* species occur in the oropharynx so a valid diagnosis of *N. gonorrhoeae* infection requires culture.

PID occurs in 10 to 40% of women with cervical gonorrhea and may be the first manifestation of infection. Symptoms often occur with the onset of menses. *N. gonorrhoeae* is the causative organism in approximately 40% of PID cases. Scarring and inflammation may result from *N. gonorrhoeae* PID even in the absence of overt symptomatology.

Fitz-Hugh–Curtis syndrome or perihepatitis associated with PID was first described with gonococcal infection, although it can be seen with *C. trachomatis* infection as well. Patients often present with right upper quadrant pain and tenderness or pleuritic pain. Treatment is supportive, often with nonsteroidal anti-inflammatory agents.

Disseminated gonococcal infection (DGI), for example, endocarditis and meningitis, occurs in 1 to 2% of patients with gonorrhea and is more common in women than in men.

Diagnosis

The diagnosis of genitourinary gonorrhea may be made with culture, microscopy, nucleic acid hybridization tests, or with NAATs. The preferred diagnostic tests are NAATs, which are fast, specific, and highly sensitive—detecting up to 98% of infections.[102] Infections at extragenital sites (e.g., rectum, pharynx, or conjunctiva) are usually diagnosed by culture because the FDA has not approved NAATs-based technology for these sites. However, laboratories may establish individual performance specifications (per Clinical Laboratory Improvement Amendments [CLIA] standards) for NAATs on nongenital samples.[1]

If culture is done, modified Thayer-Martin media should be used, and the specimen should be placed in an oxygen-free environment. Results are not usually available for 48 hours, and the sensitivity of culture to detect *N. gonorrhoeae* is lower in asymptomatic infections compared to symptomatic ones. If specimens for culture for herpes or chlamydia are being obtained concurrently, wooden or calcium alginate–based swabs should be avoided because they are toxic to these pathogens. Cultures are recommended for testing in cases of suspected or documented treatment failures in order to determine antimicrobial susceptibility.

Screenings using NAATs can be made from endocervical swabs, vaginal swabs, or urine in women, but not from urethral swabs. In women, the sensitivity of urine-based NAATs is lower compared to vaginal swab-based NAAT testing.[103] However, not all NAATs test kits are approved for vaginal swab-based testing. Results from NAATs tests are usually available within hours, and NAATs are more sensitive than culture.[104]

Nucleic acid DNA hybridization tests (e.g., DNA probes) using endocervical swabs in women are not as sensitive as NAATs-based tests.

All patients tested for *N. gonorrhoeae* infection should be tested for other STIs including chlamydia, syphilis, and HIV.

Treatment

Quinolone-resistant *N. gonorrhoeae* strains are now widely disseminated throughout the United States and the world, thus quinolones are no longer recommended to treat *N. gonorrhoeae*.[105] Only one class of antimicrobials, the cephalosporins, is recommended and available for the treatment of gonorrhea in the United States (see Tables 6.6 and 6.7). The third-generation cephalosporins are considered first-line therapy, and of these, ceftriaxone is preferred because it has demonstrated resistance less frequently compared to cefixime. Ceftriaxone is quite effective in treating oropharyngeal gonococcus, which is more difficult to cure than *N. gonorrhoeae* infections at other sites. If an injectable cephalosporin is not an option, oral cephalosporin therapy can be considered.

Management of patients who are penicillin allergic depends on the type of allergy and suspicion for true allergy. The CDC recommends the use of a cephalosporin for patients with only a history of rash and no immunoglobulin E (IgE) manifestations. Penicillin skin testing may be done to determine if the penicillin allergy is IgE-mediated. In patients with IgE-mediated penicillin allergy, azithromycin 2 g orally may be used for uncomplicated gonococcal infection, but because of concerns over emerging antimicrobial resistance to macrolides, its use should be limited. Alternatively, spectinomycin (2 g IM), if available, may be used. Spectinomycin is not available in the United States.

Approximately 10 to 30% of women with genital gonorrhea are also infected with chlamydia; therefore, the treatment regimen for *N. gonorrhoeae* infection should also include azithromycin 1 g orally or doxycycline 100 mg orally twice a day for 7 days. Patients do not require follow-up testing unless symptoms persist. Resistance testing should be performed at that time. Clinicians should advise abstinence until 7 days after initiation of treatment. Partners of infected women should be screened and treated to prevent reinfection.

Surveillance for microbial resistance in the United States is done through the CDC's Gonococcal Isolate Surveillance Project (GISP), which samples approximately 3% of all American men who have gonococcal infections. Surveillance by clinicians is also vital. Clinicians who diagnose *N. gonorrhoeae* infection in a patient with suspected cephalosporin treatment failure should perform culture and susceptibility testing of relevant clinical specimens, consult a specialist for guidance in clinical management, and report the case to CDC through state and local public health authorities.

Patients diagnosed with uncomplicated gonorrhea and who receive any of the recommended or alternative regimens do not need a test of cure 3 to 4 weeks after completing therapy. However, clinicians should advise patients with gonorrhea to be retested 3 months after treatment or whenever they next seek medical care within the following 12 months. Sexual contacts of infected persons within 60 days before onset of symptoms or diagnosis of infection in the patient should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections. Patients should abstain from sexual activity until therapy is completed and until they and their sex partners no longer have symptoms.

Pregnant women infected with *N. gonorrhoeae* should be treated with a recommended or alternate cephalosporin. For pregnant women who cannot tolerate a cephalosporin, azithromycin may be used. Patients diagnosed with *N. gonorrhoeae* infection who are HIV positive should receive the same treatment regimen as those who are HIV negative.

DGI occur in approximately 0.5 to 3% of patients and produce extragenital manifestations. It is a common cause of acute polyarthralgias, polyarthritis, or oligoarthritis in healthy, young patients. DGI is three times more common in women than men. DGI typically presents as either a triad of tenosynovitis, dermatitis, and polyarthralgias without purulent arthritis OR as a purulent arthritis without associated skin lesions. There may be overlap between these presentations. In the tenosynovitis, dermatitis, and polyarthralgic syndrome, the early stage may present with fever, chills, and malaise. The tenosynovitis often involves multiple tendons, especially those in the wrist, fingers, ankle, and toes. Skin lesions are usually painless and appear pustular or vesiculopustular. The dermatitis and tenosynovitis may spontaneously resolve, but joint involvement will usually progress unless specific treatment is given.

In the purulent arthritis without associated skin lesions syndrome, the knees, wrists, and ankles are the most commonly involved joints. More than one joint may be simultaneously infected and when polyarthritis is present, it is typically asymmetric. In patients with purulent arthritis, synovial fluid analysis is the best way to diagnose DGI. All patients with DGI should have two sets of blood cultures drawn as well as synovial, skin, urethral or cervical cultures, and rectal cultures using Thayer-Martin media.

In patients with DGI, hospitalization is recommended for initial cephalosporin-based intravenous therapy. Regimens should be continued for 24 to 48 hours after improvement is noted; after this, therapy can be switched to cefixime 400 mg orally twice daily for at least 1 week.

Mycoplasma genitalium

M. genitalium is a small prokaryocyte that has the smallest genome known in a self-replicating organism, and it acts much like a parasite. Although it is extremely difficult to culture, specific NAATs have enabled

studies to confirm it as an STI.[106,107] Because standardized diagnostic tests are not commercially available, there is currently no way to screen patients for *M. genitalium*. A recent study using two separate PCR assays found *M. genitalium* infection in 4.5% of asymptomatic women attending a sexual health clinic.[108]

M. genitalium can cause cervicitis and/or urethritis in women.[109,110] The association of *M. genitalium* with BV is controversial.

Most cases of uncomplicated *M. genitalium* urogenital infections are asymptomatic, yet *M. genitalium* is a significant cause of nongonococcal and nonchlamydial PID.[111,112] *M. genitalium* has been associated significantly with PID occurring after termination of pregnancy.[113] Symptoms associated with *M. genitalium* upper tract infections are usually mild.

M. genitalium is resistant to doxycycline, cefoxitin, and to some quinolones including ciprofloxacin, but macrolides, azithromycin in particular, and moxifloxacin have been recommended for treating infection.[114–116] Unfortunately, there is now evidence that some strains of *M. genitalium* have developed resistance to azithromycin. In one recent study, a 1.0-g single dose of azithromycin eradicated *M. genitalium* in only 67% of the patients, probably reflecting both pre-existing resistance as well as the emergence of resistance.[117] In other studies, clearance rates of 96 to 100% have been reported after treatment with 1.5-g azithromycin given over 5 days as 500 mg on day 1 followed by 250 mg once per day on days 2 to 5 in a population with a low prevalence of macrolide resistance.[118]

Because there is very little data on the natural course of *M. genitalium* infection, there are no standardized or evidence-based recommendations for treating partners. However, given the increasing recognition of the clinical importance of *M. genitalium*, treatment for partners of infected patients may be considered.

PELVIC INFLAMMATORY DISEASE

PID comprises all types of acute infections of the female upper genital tract, including cervicitis (with or without endometritis and/or salpingitis), endometritis (with or without salpingitis), salpingitis, tubo-ovarian abscesses (TOAs), and pelvic peritonitis. The highest rate of PID occurs in women 15 to 25 years of age, and women with multiple sex partners are at greatest risk. In the United States, there are approximately 100,000 office visits each year for PID.[1] A significant number of women who suffer from PID will also experience one or more long-term complications such as infertility and ectopic pregnancy. It is estimated that in a cohort of 100,000 females acquiring PID between 20 and 24 years of age, there will be 18,600 cases of chronic pelvic pain, 16,800 cases of infertility, and 8,550 cases of ectopic pregnancies.[119]

PID occurs as a result of organisms spreading from the vagina and cervix upward to the fallopian tubes and ovaries via the uterine cavity. Cervical mucus is most susceptible to ascending infection during menstruation and iron, which is abundant in the menstrual flow, may promote gonococcal growth. It is estimated that 75% of PID cases occur within 7 days of menstruation. Although polymicrobial in nature, *C. trachomatis* and *N. gonorrhoeae* have long been considered the main pathogens in PID. However, the microorganisms of the normal vaginal flora have also been associated with PID, for example, anaerobes, *T. vaginalis*, *H. influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*.[120] Similar to U.S. findings, evidence supports the idea that the role of *C. trachomatis* and *N. gonorrhoeae* as the primary causative agents of PID worldwide is decreasing.[121]

The role of anaerobes in PID has long been established.[122] BV is more common among women with PID, but it has not been shown to be solely responsible for PID. Evidence shows that *M. genitalium* is associated with nongonococcal and nonchlamydial PID and has been shown to be associated with tubal infertility.[112] For clinical purposes, the microbiology of PID should be viewed and treated as a mixed (facultative and anaerobic) polymicrobial infection.

Of the causative organisms for PID, *C. trachomatis* infection carries the highest risk of infertility. When the inflammatory infection reaches the fallopian tube, it causes epithelial degeneration and deciliation of ciliated cells along the fallopian tube mucosa. During endosalpingitis, edema increases intraluminal agglutination causing a clubbing effect of the fallopian tube, which results in infertility or ectopic pregnancy. Repeated episodes of PID are associated with declines in pregnancy rates and live births. Pregnancy rates after one, two, or three or more episodes of PID were 89, 77, and 46%, respectively, whereas the cumulative proportions of women achieving a live birth after mild, moderate, and severe PID were 90, 82, and 57%, respectively.[123] The ratios of ectopic pregnancy to intrauterine pregnancy after one, two, and three episodes of PID are estimated at 1:15, 1:6, and 1:3, respectively, whereas in the case of a single episode of mild, moderate, or severe PID, the rates are estimated at 1:35, 1:25, and 1:5, respectively.[124]

Patients diagnosed with PID are also at an increased risk of recurrent infection because one in four will have a recurrence. Adolescents are 50% more likely to have a recurrence than adult women.[125]

As many as one-third of women with PID develop chronic pelvic pain, which may be related to scarring and adhesions that from in response to the inflammation.[123] Recurrent PID appears to be the strongest predictor for the development of chronic pelvic pain.[126]

There is some evidence that PID may increase the risk for ovarian cancer, and the risk may be highest in those with recurrent episodes of PID.[127,128] The correlation is not clear, however, because PID increases the risk for other known risk factors for ovarian cancer such as nulliparity or low parity, low gravidity, and infertility.

Barrier methods of contraception have demonstrated protection against PID, with condoms providing the best protection against endocervical chlamydia and gonorrhea. Although the use of oral contraceptives is associated with a two-fold increase in the prevalence of *C. trachomatis* and *N. gonorrhoeae* infections, their use is also associated with a 50% reduction in the risk of PID. This may be due to a diminution of PID-associated symptoms as well as tissue damage.

Intrauterine devices (IUD) cause little increased risk of PID, and this risk is primarily limited to the time of insertion and first 3 weeks after initial insertion.[129] Infections more than 1 month after insertion are generally due to a newly acquired STD. Some evidence shows that women with clinical signs or symptoms consistent with IUD should receive appropriate antibiotic therapy, but IUDs do not need to automatically be removed in patients with PID.[130] The CDC notes that there is insufficient evidence to mandate removal of an IUD when a woman is diagnosed with acute PID, but close clinical follow-up is recommended. In the only randomized controlled trial on this issue, there was evidence that in places where a replacement IUD was readily available, antibiotics should be initiated with removal of the IUD to follow shortly thereafter in order to increase the rate of clinical improvement of mild to moderate PID.[131] If the IUD is removed, a new one may be inserted 3 months after the infection has resolved.

Patients who have undergone tubal ligation remain susceptible to the clinical syndrome of PID. Although it is uncommon, it is possible to see PID in the first 12 weeks of pregnancy prior to maturation of the decidual seal and formation of the mucus plug of pregnancy.

Clinical Symptoms

The presenting signs and symptoms of PID are quite variable. Typically, the clinical features of PID may include fever (temperature higher than 100.4°F), bilateral lower abdominal/pelvic pain, and a mucopurulent discharge. Abnormal uterine bleeding may also occur in women with PID. Only about half of women with PID are febrile, and the lower abdominal pain may be so mild as to be overshadowed by other lower genital tract symptoms, for example, vaginal discharge or abnormal bleeding.[132] Abdominal tenderness may not present in many patients with PID, particularly if peritonitis is not present or if there is endometritis without salpingitis. Rebound tenderness and decreased bowel sounds are common. Significant tenderness in the right upper quadrant does not exclude PID because approximately 10% of these patients have perihepatitis.

On pelvic exam, cervical/uterine motion tenderness and adnexal tenderness may be present. The findings of a purulent endocervical discharge and/or acute cervical motion and adnexal tenderness with bimanual examination are strongly suggestive of PID. The rectovaginal exam should confirm that the uterus and adnexa are the foci of tenderness.

Diagnosis

Clinicians should maintain a low threshold for diagnosing PID because there is no single historical, physical, or laboratory finding that is both sensitive and specific for the diagnosis of acute PID[133] (see Table 6.8 for diagnostic criteria considerations for diagnosing PID). Risk factors and clinical signs and symptoms are poor predictors of PID, in part due to the wide variety of signs and symptoms that may be present. The positive predictive value (PPV) of clinical diagnosis is 65 to 90% compared to laparoscopy, and this value increases in settings where chlamydia and gonorrhea rates are high, in patients younger than 25 years of age, and in patients attending STI clinics.[134]

Vaginal wet smears are found to have a high sensitivity for upper genital tract infection (87 to 91%) if three or more WBCs are seen per high-power field, whereas the absence of WBCs on a vaginal wet smear has a high negative predictive value (94.5%).[135] Hence, if the cervical discharge is normal and there are no WBCs on the vaginal wet prep, the likelihood of PID is very low, and alternative diagnoses should be considered.

Endometrial biopsy (EMB) showing histopathologic signs of endometritis (plasma cell endometritis) is a component of PID but is nonspecific. Bacterial cultures made from intracervical or intrauterine samples can adequately identify pathogens in nongonococcal and nonchlamydial PID.

Transvaginal sonography is useful to assess the presence of a TOA. Power Doppler ultrasound is able to detect changes in blood flow associated with tubal inflammation, and according to a small study, has an

TABLE 6.8 Diagnostic Considerations for Pelvic Inflammatory Disease

Minimum criteria for initiation of empiric therapy in women at risk include the following:

- Uterine/adnexal tenderness *or*
- Cervical motion tenderness
- No other identified cause of illness

One or more of these increases the specificity of the diagnosis:

- Fever (oral temperature >101°F [>38.3°C])
- Abnormal cervical or vaginal discharge
- Presence of white blood cells in vaginal discharge
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory proven infection with NG or CT

Specific criteria for diagnosing PID may also include the following:

- EMB with histopathologic evidence of endometritis
- Transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)
- Laparoscopic abnormalities consistent with PID including erythema, edema, and purulent exudate

From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010*. Atlanta, GA: U.S. Department of Health and Human Services; 2011.

overall accuracy over 90% in diagnosing PID.[136] Larger studies are needed to assess the usefulness of this technique in clinical practice.

Laparoscopy remains the gold standard in diagnosing salpingitis and should be performed whenever diagnosis is difficult or if there is a lack of clinical response after a few days of treatment. Laparoscopy has several limitations in the diagnosis of PID because it cannot detect endometritis and may not detect subtle inflammation of the fallopian tubes. Not all cases of PID include salpingitis so if laparoscopy is negative but clinical suspicion is still high, EMB is indicated for diagnostic purposes.

COMPLICATED PELVIC INFLAMMATORY DISEASE

Complicated PID is characterized by TOAs and pelvic peritonitis. Both are serious and potentially life-threatening conditions. Approximately 15 to 30% of women with PID have concurrent TOAs.[137] Aggressive medical and/or surgical therapy is indicated, and rupture or leakage of a TOA may incur sepsis. Rupture of TOAs occurs in approximately 15% of cases.[138]

Although patients may present with acute pelvic pain and fever, not all patients with TOAs present in an acute fashion. On clinical exam, a painful, adnexal mass may be palpated in TOA and signs of peritonitis are present in cases of pelvic peritonitis. Transvaginal sonography, radiologic imaging, pelvic ultrasound, and/or computed tomography (CT) scan may be used to confirm the diagnosis of TOA. WBC count and erythrocyte sedimentation rate are recommended in patients with clinically severe PID.

TOAs may occur in postmenopausal women and are associated with an increased risk for concurrent malignancy; thus, surgical therapy and intervention is warranted.[139]

Treatment

The goal of PID treatment is to prevent infertility, ectopic pregnancy, and other long-term sequelae associated with PID (see Fig. 6.1 for suggested management of PID). The effectiveness of therapy in preventing infertility is contingent on the time between onset of symptoms and the initiation of treatment. The CDC recommends empiric therapy for PID in sexually active women and for women at risk for PID who present with pelvic or lower abdominal pain, where no cause other than PID can be identified, and who have one of the following present on pelvic examination: cervical motion tenderness or uterine tenderness or adnexal tenderness.[1]

Most cases of PID can be treated as outpatients, and up to 80 to 90% of women are treated as outpatients.[140] Comparing effectiveness of therapy with reproductive outcomes, the PID Evaluation and Clinical Health (PEACH) study showed no difference between inpatient and outpatient treatment in women with mild to moderate PID.[123] However, severe and complicated cases of PID must be hospitalized (Table 6.9). Adolescents should be managed according to the same guidelines for adult women. If a patient is being treated as an outpatient, a repeat physical examination within 24 to 72 hours is warranted to verify response to therapy. If there is no improvement within 72 hours, the diagnosis should be confirmed and parenteral treatment should be initiated.

TABLE 6.9 Recommendations for Hospitalization of Patients With Pelvic Inflammatory Disease

- Surgical emergencies (e.g., appendicitis) cannot be excluded.
- Patient is pregnant.
- Patient has not responded clinically to oral antimicrobial therapy.
- Patient is unable to follow or tolerate an outpatient oral regimen.
- Patient has severe illness, nausea and vomiting, or high fever.
- Patient has a tubo-ovarian abscess.

From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010.* Atlanta, GA: U.S. Department of Health and Human Services; 2011.

PID treatment regimens must provide empiric, broad-spectrum coverage of likely pathogens. The outpatient and inpatient regimens recommended by the CDC are reviewed in Table 6.10 and Table 6.11, respectively. For women with PID of mild or moderate severity, parenteral and oral therapies appear to have similar efficacy for short- and long-term outcomes. All regimens for PID must include coverage for *C. trachomatis* and *N. gonorrhoeae* because negative endocervical testing for these organisms will not rule out upper genital tract infection with them. Due to increasing resistance, fluoroquinolones are no longer recommended in the United States for the treatment of gonorrhea or associated conditions such as PID. Some form of coverage for anaerobic infections may also be considered.

In European countries, oral moxifloxacin (400 mg once a day) has been approved for the treatment of PID since 2008 and is a good substitute for the CDC recommended regimens, as shown in clinical trials.[141]

TABLE 6.10 Outpatient Treatment of Pelvic Inflammatory Disease

Ceftriaxone (Rocephin) 250 mg IM in a single dose
or
Cefoxitin (Mefoxin) 2 g IM plus probenecid 1 g orally administered concurrently in a single dose
or
Other parenteral third-generation cephalosporin (e.g., ceftizoxime [Cefizox] or cefotaxime [Claforan])
plus
Doxycycline (Vibramycin, Doryx) 100 mg orally twice a day for 14 d
with or without
Metronidazole (Flagyl) 500 mg orally twice a day for 14 d

From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010.* Atlanta, GA: U.S. Department of Health and Human Services; 2011.

TABLE 6.11 Inpatient Treatment of Pelvic Inflammatory Disease

Regimen A

Cefotetan (Cefotan) 2 g IV every 12 h *or* cefoxitin (Mefoxin) 2 g IV every 6 h

plus

Doxycycline (Vibramycin) 100 mg orally or IV every 12 h

Regimen B

Clindamycin (Cleocin) 900 mg IV every 8 h

plus

Gentamicin (Garamycin) loading dose IV or IM (2 mg/kg of body weight) followed by a maintenance dose (1.5 mg/kg) every 8 h. Single daily dosing may be substituted.

Alternative parenteral regimens

Ampicillin/sulbactam (Unasyn) 3 g IV every 6 h *plus* doxycycline (Vibramycin, Doryx) 100 mg orally or IV every 12 h.

These regimens are to be used until at least 24 h after the patient demonstrates substantial clinical improvement. They may then be changed to doxycycline (Vibramycin) 100 mg orally two times a day for a total of 14 d of treatment. If tubo-ovarian abscess is present, many health care providers use clindamycin (Cleocin) 900 mg orally three times a day or metronidazole 500 mg twice a day for continued therapy with doxycycline.

From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010*. Atlanta, GA: U.S. Department of Health and Human Services; 2011.

The efficacy of both parenteral and oral regimens has been supported by randomized clinical trials.[123] To increase coverage of anaerobic bacteria, metronidazole may be added if the patient has a pelvic abscess, proven or suspected infection with *T. vaginalis* or BV, or a history of gynecologic instrumentation 2 to 3 weeks prior to infection. Transition from parenteral to oral therapy may be started after 24 hours of sustained clinical improvement, for example, resolution of fever, nausea, vomiting, and severe abdominal pain. Clinical signs of improvement should be seen within 3 days of initiating therapy. Oral doxycycline is recommended for both oral and parenteral regimens due to the association of pain and burning with parenteral administration.

Although the optimal duration of oral therapy is not known, most regimens call for a 2-week course of therapy. A review at 4 weeks post-therapy is useful to ensure an adequate clinical response to treatment and compliance with oral antibiotics. Follow-up testing at 3 to 6 months is recommended in patients diagnosed with chlamydia or gonorrhea.

The choice of antibiotic therapy in cases of PID and accompanying TOAs depends on the patient's status and characteristic of the abscess. Suspected intra-abdominal rupture of a TOA is a life-threatening emergency and requires prompt surgical intervention. Antibiotic therapy alone is effective for approximately 70% of all TOAs.[142] TOAs larger than 9 cm have a high likelihood of requiring surgical intervention, approximating 60%.[143]

In patients who do not respond to antibiotic therapy after 24 to 72 hours, surgical drainage by laparoscopy is needed to allow division of adhesions and effective drainage of TOA. Image-guided drainage of TOAs is less invasive and is also effective with success rates of 70 to 100%.[144-146] It is an appropriate choice for patients with TOAs who do not worsen on antibiotic therapy alone but yet clearly fail to improve as well. Continued antibiotics are indicated before, during, and after any minimally invasive or surgical procedures for TOAs.

Sexual partners should also be examined, tested, and treated with a regimen appropriate for both uncomplicated gonorrhea and chlamydia. To avoid reinfection, patients and sexual partners should abstain from sexual intercourse until completion of therapy.

OTHER SEXUALLY TRANSMITTED DISEASES AND INFESTATIONS

The following infections are discussed in other chapters: trichomoniasis (Chapters 4 and 14), genital warts (Chapters 5 and 14), and pediculosis pubis (Chapter 14).

VACCINE-PREVENTABLE SEXUALLY TRANSMITTED INFECTIONS

Hepatitis B

Hepatitis B is caused by infection with the HBV. The incubation period of HBV is approximately 6 weeks to 6 months. HBV is primarily found in blood, with lower concentrations in wound exudates, semen, vaginal secretions, and saliva (CDC).[1] HBV is highly infectious and remains relatively stable in many environments. HBV infection can be self-limited or chronic. Acute liver failure and death occurs in approximately 1% of cases, and in chronic HBV infection, the risk for premature death from cirrhosis or hepatocellular carcinoma (HCC) is 15 to 25%.[1] Transmission occurs when mucosal surfaces are exposed to blood or body fluids that contain blood. Risk factors include having unprotected sex with an infected partner or more than one partner, or having a history of other STIs. Neonatal transmission can also occur. The most effective preventive methods against HBV infection are the hepatitis B vaccination and hepatitis B immune globulin (HBIG). The CDC recommends hepatitis B vaccination for all unvaccinated adolescents, all unvaccinated adults at risk for HBV infection, and all adults seeking protection from HBV infection.[1]

Clinical Symptoms

Approximately half of newly acquired HBV infections are symptomatic in adults. Symptoms of HBV infection are indistinguishable from hepatitis A and C. The clinical manifestations of HBV infection include dark urine, appetite loss, fatigue, nausea and vomiting, itching, jaundice, pale-colored stools, and abdominal

pain over the location of the liver. Fulminate hepatitis is a life-threatening complication of acute infection although rare.

Diagnosis

Serologic testing is required for diagnosis of acute or chronic HBV infection. See Table 6.12 for interpretation of serologic tests for HBV infection. Viral load can be assessed using HBV DNA tests, which is useful for monitoring patient responses to antiviral therapy. Liver function tests may be used to assess liver damage.

Treatment

There is no specific therapy for patients with acute hepatitis B infection. Patients typically require rest and should avoid alcohol, fatty foods, and any medications that may cause liver damage or are metabolized in the liver. Patients presenting with nausea and vomiting may require hospitalization. Patients with fulminate hepatitis or signs of liver damage require hospitalization. Patients diagnosed with chronic hepatitis B infection should be referred to a specialist in CLD. Although medications are not typically used to chronic infection, treatment may be initiated if viral load is elevated or if liver damage occurs. Nucleoside/nucleotide analogues and interferons have been approved by the FDA to treat hepatitis B and are effective at suppressing replication and result in remission of liver disease in some patients. HCC screening is recommended by the CDC in patients with chronic HBV infection.[1]

Human Papillomavirus

See Chapters 5 and 14.

Other Considerations for Sexually Transmitted Infections

Douching

Vaginal douching is done by placing a liquid medium, for example, water, baking soda, Betadine, or a commercially available product, into the vagina, often for purposes of hygiene. It is estimated that nearly one in three women in the United States practices vaginal douching.[147] The practice of douching is inversely related to education, regardless of race. Many women begin in adolescence based on the advice of their mothers or other family members.[148]

Many women believe douching has no serious risks, and among adolescents, there is a belief that it will prevent STIs.[149] There are no known health benefits with douching, but evidence suggests that douching may increase susceptibility to acquisition of HIV and other STIs and, possibly, PID.[150,151]

Douching may increase the risk for STI acquisition by washing away lactobacilli that produce hydrogen peroxide (H_2O_2), which decreases the level of acidity in the vagina. These changes result in an imbalance in the normal bacterial flora of the vagina and diminished CD4 lymphocyte activation. These changes increase susceptibility to STI pathogens.[150,152] Patients should be advised that there is no medical or health indication for douching, and it should be avoided.

Sexual Assault

Sexual assault is any sexual act performed by one person on another without consent. It may occur with the use of force, threat of force, or in instances where the victim cannot give consent. The lifetime prevalence for sexual

TABLE 6.12 Interpretation of Serologic Test Results for Hepatitis B Virus Infection

Serologic Marker				
HBsAg	**Total Anti-HBc**	**IgM Anti-HBc**	**Anti-HBs**	**Interpretation**
−	−	−	−	Never infected
+[a]	−	−	−	Early acute infection; transient up to 18 d after vaccination
+	+	+	−	Acute infection
−	+	+	−	Acute resolving infection
−	+	−	+	Recovered from past infection and immune
+	+	−	−	Chronic infection
−	+	−	−	False positive (i.e., susceptible); past infection; "low-level" chronic infection[b]; passive transfer to infant born to HBsAg-positive mother
−	−	−	+	Immune if concentration is >10 mIU/mL, passive transfer after HBIG administration

HbsAg, hepatitis B surface antigen; Anti-HBc, antibody to hepatitis B core antigen; IgM, immunoglobulin M; Anti-HBs, antibody to HbsAg; HBIG, hepatitis B immune globulin.
[a]To ensure that an HBsAg-positive test result is not a false positive, samples with repeatedly reactive HBsAg results should be tested with an FDA-cleared (and, if appropriate, neutralizing confirmatory) test.
[b]Persons positive for only anti-HBc are unlikely to be infectious except under unusual circumstances involving direct percutaneous exposure to large quantities of blood (e.g., blood transfusion and organ transplantation).
From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010.* Atlanta, GA: U.S. Department of Health and Human Services; 2011.

assault for women in the United States is estimated to be 18%.[153] Only 10 to 15% of all sexual assaults will be reported.

The assessment of sexual assault victims includes the following:

Assessment and treatment of physical injury with special focus on the genitalia
Psychological assessment and support
Pregnancy assessment and prevention
Evaluation, treatment, and prevention of STIs
Forensic evaluation

The focus here will be on the evaluation, treatment, and prevention of STIs. Sexual assault cases should be evaluated by providers who have been specially trained; however, other providers may conduct the evaluation if:

A trained provider is not available
Patient prefers that the examination be done by another provider and cannot be dissuaded
Evaluation is occurring later than the locally determined interval for formal evidence collection, which varies from 3 to 7 days

Evaluations should be conducted in a manner that minimizes further trauma to the sexual assault survivor and a chaperone or advocate should be present. It is recommended that providers not force evaluation or treatment and allow the victim some control during the process. Details of the assault need to be included in the patient history for forensic purposes. The physical examination should focus on the breasts, external genitalia, vagina, anus, and rectum. The posterior vagina and labia minora are common sites of vaginal injury.

Testing for STIs in sexual assault cases is controversial because positive tests are not required for prosecution and may be used by the defense as evidence of promiscuity. However, all 50 states have laws banning the evidentiary use of a survivor's sexual history including the presence of previous STIs.[1] Testing may be forgone if patients plan to take prophylactic treatment for infections.

Trichomoniasis, BV, gonorrhea, and chlamydia are the most frequently diagnosed infections in women who have been sexually assaulted.[1] These conditions are fairly prevalent so their presence after an assault does not necessarily imply acquisition during the assault. The risk of chlamydial infection is estimated to be 3 to 16%, with an 11% risk of PID and BV and a 7% risk of trichomoniasis.[154]

Diagnostic tests may include NAATs for *C. trachomatis* and *N. gonorrhoeae* from any site of contact, including specimens from the vagina, rectum, pharynx, and/or mouth.[1] A wet mount and culture can be used to detect *T. vaginalis*, BV, and candidiasis. Serologic testing can be used to detect HIV, hepatitis B, and syphilis and can be repeated at 6 weeks, 3 months, and 6 months if results are negative. Repeat testing for STIs should occur 1 week after the assault if treatment was not provided to the patient or if patients on therapy become symptomatic. Pregnancy testing should be done for women of childbearing capability.

Postexposure prophylaxis (PEP) is recommended by the CDC because compliance with follow-up is poor in sexual assault survivors (Table 6.13). Postexposure hepatitis B vaccination without HBIG should be administered at the time of initial examination and at 1 to 2 and 4 to 6 months after the first dose. Because data is limited regarding the efficacy of this hepatitis B vaccination without HBIG, many programs continue to use HBIG as prophylaxis in addition to vaccination. Vaccination is not necessary in patients with previous hepatitis B vaccine and documented immunity. Empiric antimicrobial therapy for chlamydia, gonorrhea, and trichomoniasis should be initiated. Emergency contraception is recommended for patients of reproductive capability. Patients should abstain from sexual intercourse until prophylactic treatment is completed and consider condom use until serologic testing is completed.

The risk of HIV transmission in consensual vaginal intercourse is 0.1 to 0.2%, and for rectal intercourse, it is 0.5 to 3%.[155] The risk of transmission after sexual assault depends on the specific circumstances of the assault (e.g., bleeding, which often accompanies trauma, or vaginal, anal, or oral penetration). If ejaculation occurs, the site of ejaculation, viral load of the ejaculate, and the presence of a STI or genital lesions in the assailant or survivor will affect the risk for HIV transmission. Antiviral drugs should only be initiated within 72 hours of exposure. PEP with zidovudine is associated with a reduced risk of acquiring HIV.[156] The CDC recommendations for postexposure assessment of children, adolescents, and adult survivors of sexual assault are available in Table 6.13.

After the initial examination, follow-up examinations are recommended to (a) detect new infections acquired during or after the assault; (b) complete hepatitis B vaccination, if indicated; (c) complete counseling and treatment for other STDs; and (d) monitor side effects and adherence to postexposure prophylactic medication, if prescribed.[1]

TABLE 6.13 Recommended Regimens for Victims of Sexual Assault

Ceftriaxone 250 mg IM in a single dose
OR
Cefixime 400 mg orally in a single dose
PLUS
Metronidazole 2 g orally in a single dose
PLUS
Azithromycin 1 g orally in a single dose OR doxycycline 100 mg orally twice a day for 7 d

From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Treatment Guidelines, 2010*. Atlanta, GA: U.S. Department of Health and Human Services; 2011.

CLINICAL NOTES

- Primary outbreaks of herpes are often asymptomatic. Eighty percent of patients will suffer a recurrent outbreak the year following the primary outbreak.
- The risk of neonatal infection with herpes is highest in mothers with an initial outbreak at or around the time of delivery. For recurrent maternal infections, the risk of fetal transmission is much lower.
- Acyclovir, famciclovir, and valacyclovir may be used prophylactically to reduce the frequency and severity of recurrences.
- Syphilis may present in any fashion and in any organ system. The primary ulcer is painless.
- After treatment for syphilis, titers should be followed for 1 to 2 years to ensure adequate therapy and/or detect reinfection.
- LGV is caused by *Chlamydia* and is a painless ulcer in the early stages. If untreated, it results in fistulas, strictures, and elephantiasis.
- Chancroid, caused by *H. ducreyi*, causes a painful ulcer and subsequent bubo formation.
- CT infection is often asymptomatic; therefore, adequate detection depends on screening using a NAAT.
- Chlamydia infection is associated with PID, tubal damage, infertility, and chronic pain.
- Gonorrhea is very contagious and can induce acute PID. Due to a steady increase of fluoroquinolones-resistant *N. gonorrhoeae*, the current recommended regimen is ceftriaxone.
- When treating gonorrhea, a regimen effective against *C. trachomatis* should also be given because these two infections are often concurrent.
- PID is frequent in women of reproductive age in the United States. It is also a significant cause of infertility, chronic pelvic pain, and increased risk of ectopic pregnancy.
- Diagnosis of acute PID is essentially based on clinical signs (cervical motion/uterine pain, adnexal tenderness, mucopurulent cervical discharge) and bacteriologic exams.
- PID treatment regimens must provide empiric, broad-spectrum coverage of likely pathogens.
- Genital warts are due to papillomavirus. They are very frequent in young women. Up to 20% of patients will have spontaneous resolution. Otherwise, both medical and surgical modalities exist to treat it.

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CHAPTER 7

Chronic Pelvic Pain

John F. Steege

Chronic pelvic pain (CPP) is generally defined as pain present in the pelvis, more often than not, for 6 months or longer. It may be cyclic or continuous in nature. Pain that is present at least 5 days/month occurs in 12% of women of reproductive age and is the reason for hysterectomy in approximately 12% of such procedures.[1,2] Approximately half of all operative laparoscopies are performed to investigate problems with pain, many of those chronic in nature.[3,4] The surgically minded clinician may conclude that once any pathology is found, the source of the pain has been found as well. The point of this chapter is to suggest a more thoughtful consideration of pain as a disease rather than as solely a symptom of pathology.

As a multifactorial disease, CPP often challenges the best of clinicians. When organic pathology is detected, its precise relationship to the production of symptoms is often uncertain. The longer the pain has gone on, the more likely treatment will be prolonged and perhaps incompletely successful. For the surgically oriented gynecologist, this problem can be especially frustrating. Surgical solutions are not always apparent, and pain may persist despite a satisfactory anatomic result. The challenge for the gynecologist is to learn when traditional gynecologic medical and surgical treatments will work and when they are less likely to succeed.

The temptation to resort to surgery is inherent in gynecologic training. The few placebo-controlled trials of surgery that have been carried out have demonstrated substantial nonspecific (placebo) effects of surgery, which can occur in 65 to 100% of cases and may last as long as a year.[5,6] The surgeon seeing the patient 4 to 6 weeks after surgery may witness partial or complete relief of pain, only to see it return 3 to 12 months later and assume this must represent a return of disease. The most egregious example of this from my own practice is a 39-year-old woman who, prior to my evaluation, had undergone 37 laparoscopies to treat her pelvic pain. Each had been followed by 3 to 6 months of pain relief, although minimal intervention was done each time; she still had all reproductive organs in place.

This review focuses on information about pain pathways that may help to explain some of these phenomena. It reviews basic elements of history and physical examination pertinent to the various diagnoses and sources of CPP. Current treatments for each disorder are summarized. More importantly, we also deal with the cases in which treatment of apparent pathology is unsuccessful in relieving pain.

PATHWAYS OF PAIN PERCEPTION

Put simply, clinical pain falls into two categories: (a) nociceptive pain, caused by true peripheral tissue damage or physiologic processes, and (b) centralized pain, sometimes called "neuropathic," which continues with very little or no input from damaged peripheral tissues, and is presumed to be related to damage to or dysfunction of the peripheral or central nervous system (CNS). Treatments aimed at peripheral tissues, whether medical or surgical, are more likely to be helpful when the pain is truly nociceptive. Conversely, centralized/neuropathic pain will not respond to these measures (beyond the placebo effect) but will only yield to pharmacologic and other nonsurgical measures that target CNS processes.

Before describing the typical clinical hallmarks of these two basic types of pain, a review of pain neurophysiology is in order. Nociceptive signals emerging from pelvic visceral structures travel cephalad through one or more of several routes.[7] ("Nociceptive signals" are peripheral nerve impulses that are destined to produce negatively perceived sensations; "pain" is a brain interpretation of sensations indicative of real or potential tissue damage.) Sympathetic afferent signals arising from the uterus, cervix, and immediately adjacent portions of the uterosacral, broad, and round ligaments travel via the inferior and superior hypogastric plexuses to the sympathetic chain. From there, they go to the T10 to T12 levels of the spinal cord. Additional sensation may be provided through the nervi erigentes, or pelvic nerves, which cross the pelvic floor and ultimately join the S2 to S4 segments of the spinal cord. Fibers from both the sympathetic and parasympathetic systems traverse Frankenhäuser plexus and the uterovesical ganglion.

The gate control theory, developed by Melzack and Wall in the 1950s and early 1960s, provides a model to help explain some of the variability in clinical pain patterns.[8] It is a useful model of integration

of physical and psychological processes into a single scheme. The major contribution of this theory was to suggest that higher centers in the brain have the capacity to *physiologically* down- or upregulate signals that approach the spinal cord. This regulation may determine the degree to which peripheral nociceptive signals travel cephalad to reach conscious perception.

Building on this theory, further neurophysiologic research has focused on these spinal cord mechanisms.[9] Glial cells, once thought to have only a nutritive role for surrounding neurons, are now recognized as playing a major role in this modulation process.[10] Uncontrolled activation of microglial cells under neuropathic pain conditions induces the release of proinflammatory cytokines (interleukin [IL]-1β, IL-6, tumor necrosis factor) and complement components that facilitate pain transmission. Microglial activation can lead to altered activity of opioid systems, and neuropathic pain is characterized by resistance to morphine.[10]

It is now known that there are several categories of narcotic receptor sites both in the brain and the spinal cord. Indeed, some inhibit pain perception, whereas others actually facilitate it, giving rise to narcotic-induced hyperalgesia. In addition, the spinal cord appears to have receptors for local anesthetics and numerous other neurotransmitter-like substances, including cannabinoids.

Many researchers in pain have found the gate theory too limiting as well. Melzack[11] suggested the term "neuromatrix" to describe a weblike set of communications, ascending and descending, that are involved in nociception and ultimately, in the perception of pain. The model allows inclusion of multiple new factors that have been the foci of recent research on spinal cord and central elements of the pain perception system. For example, recent evidence has begun to highlight the role of neuroimmune activation following tissue injury as an important mechanism in the development of chronic pain via cytokine-mediated central sensitization of neural pathways.[12]

Clinically, centralized pain is typically present continuously, is intense, and often is described as burning in nature. The patient may demonstrate sympathetic activation manifested by tachycardia, hypertension, hyperhidrosis, and insomnia. When examined, she may demonstrate hyperalgesia (excessive response to noxious stimuli) and/or allodynia (painful response to nonpainful stimuli).

Spinal cord "wind-up" occurs when repeated, low-level nociceptive stimuli from the periphery elicit progressively more dramatic responses from second-order neurons at the spinal cord level even though the intensity of the stimuli may remain constant or even be diminished. This phenomenon has been well demonstrated in acute pain models at the animal level.[13] There is considerable speculation regarding the impact of this process on chronic pain symptoms. When examining a patient with pain, the tendency for repeated examination to elicit pain from initially nontender areas is a phenomenon consistent with "wind-up."

It has also long been observed that visceral organs and portions of the somatic system often share nerve supply from the same level of the spinal cord. Pain from viscera may thus be referred to the appropriate somatic dermatome, a process labeled viscerosomatic convergence. With time, however, stimuli applied to somatic structures may sometimes reproduce a nociceptive response perceived as though it emanated from the original offending viscus. For example, pain from a vaginal fornix in a posthysterectomy patient can be referred to a relatively localized area of the abdominal wall. Typically, this spot is about 5 cm cephalad to the inguinal ligament and 5 cm from the midline toward the symptomatic side. With time, this abdominal wall area may itself become intrinsically tender. Palpation of this spot may reproduce the vaginal apex pain. Interestingly, local anesthetic block of the abdominal wall tender spot (trigger point) can decrease the sensitivity of the vaginal apex.

There are complex interactions among the reproductive organs, the urinary tract, and the colon. One phenomenon associated with these interactions is viscerovisceral hyperalgesia. In this condition, inflammation or congestion in an organ (e.g., the reproductive organs) enhances pain in viscera, skin, or muscle that share common spinal cord segments.[14–16]

Although acute and chronic pain are quite different physiologic processes, some lessons learned from acute pain management apply well to the management of chronic pain. For example, studies regarding the impact of preemptive analgesia on acute postoperative pain suggest that the ideal postoperative pain regimen is multifaceted. The ideal regimen simultaneously interrupts the nociceptive signals at the peripheral tissue level, blocks receptor sites within the spinal cord, and alters the central perception of pain.[17] In many chronic pain conditions, this would also be the ideal regimen. Treatments need to be applied at the peripheral tissue level and include pharmacologic measures directed toward spinal cord and central mechanisms as well.

All chronic pain is profoundly influenced by psychological processing and responses.[18] Patients with identical diseases will vary greatly in pain severity, functional impairment, and pain behaviors.[19] Operant conditioning factors[20] and cognitive behavioral factors[21] may be important in the maintenance of chronic pain behaviors.

Chronic pain is also influenced by psychosocial and psychiatric disturbances such as cultural influences, social support, comorbid mood disorder, and drug abuse.[22] The contribution of psychological, social, and psychiatric factors should not lead to the conclusion that a pain syndrome is primarily psychogenic. Pain related

exclusively or primarily to psychological factors occurs but is far less prevalent than pain associated with organic processes that are powerfully influenced by psychosocial mediators and psychiatric comorbidities.

EVALUATION OF CHRONIC PAIN SYNDROMES

History

Before launching into the clinical evaluation of CPP, it is important to point out that the examiner should begin the effort with a specific purpose in mind: to make a list of possible contributing factors to a person's pain. This may sound simple, but it is in fact a radical departure from the traditional organ-based conceptualization of chronic pain. It recognizes that individual organs are not served by completely separate neural pathways. Rather, they are served by a highly overlapping network, which makes it likely that multiple organ systems may participate in the pain, as opposed to a single dysfunction organ system bearing the entire responsibility for the pain.

This list of contributing factors is made on the basis of a careful and detailed clinical history. Physical examination supplies additional detail(s) and confirmation of diagnoses, but in the majority of cases, if uncertainty remains, more historical questions need to be asked. A very detailed history enables the physician and patient to formulate a well-designed set of interventions. Even if surgery seems needed, simultaneous treatment of other components is more likely to result in good outcome. (The International Pelvic Pain Society has developed a detailed history and physical examination form for evaluating women with CPP. It may be freely reproduced and used as long as the copyright notice on the form remains intact. Because the form is 11 pages long, it is not reproduced in its entirety in this text, but it may be found at http://www.pelvicpain.org/pdf/History_and_Physical_Form/IPPS-H&PformR-MSW.pdf or, alternatively, by going to the International Pelvic Pain Society website at http://www.pelvicpain.org/ and locating it in the valuable resources section.)

The history of the present illness should include the character, intensity, and radiation of the pain; the relationship of the pain to the menstrual cycle; and the daily chronologic pattern of the pain. A standard method of quantifying pain severity using either a visual analog or numerical rating system should be used to measure pain over time. Having the patient keep a monthly pain calendar may also be useful in assessing her response to treatment (Fig. 7.1). Asking the patient to complete a pain map can be helpful for localizing pain (Fig. 7.2). Information regarding previous medical therapies and their associated side effects, and previous procedures and their effect(s) on the pain pattern(s) should be garnered. Some useful generalizations about pain patterns associated with particular kinds of pelvic pathology are listed in Table 7.1.

When pain is prolonged and chronic, it may remain confined to its original site and intensity. All too often, however, the anatomic site of the pain becomes less distinct, and symptoms originating in surrounding organ systems may join the original complaint. For example, a woman who starts with a problem limited to endometriosis may develop functional bowel symptoms as well as discomforts related to excessive contraction of the pelvic floor musculature. As mentioned previously, nociception from a painful posthysterectomy vaginal apex may refer to the lower abdominal wall on the side of the involved fornix. When taking a history of a chronic pain problem, it is useful to pay attention to the precise chronology of the addition of each component

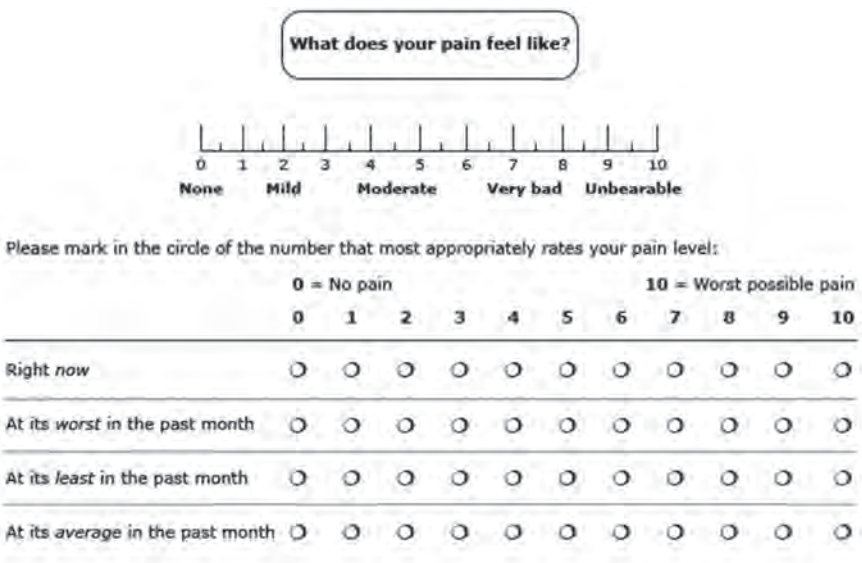

FIGURE 7.1 Monthly pain scale. (From Howard F. Evaluation of chronic pelvic pain in women. UpToDate Web site. http://www.uptodate.com/contents/evaluation-of-chronic-pelvic-pain-in-women. Accessed November 25, 2013.)

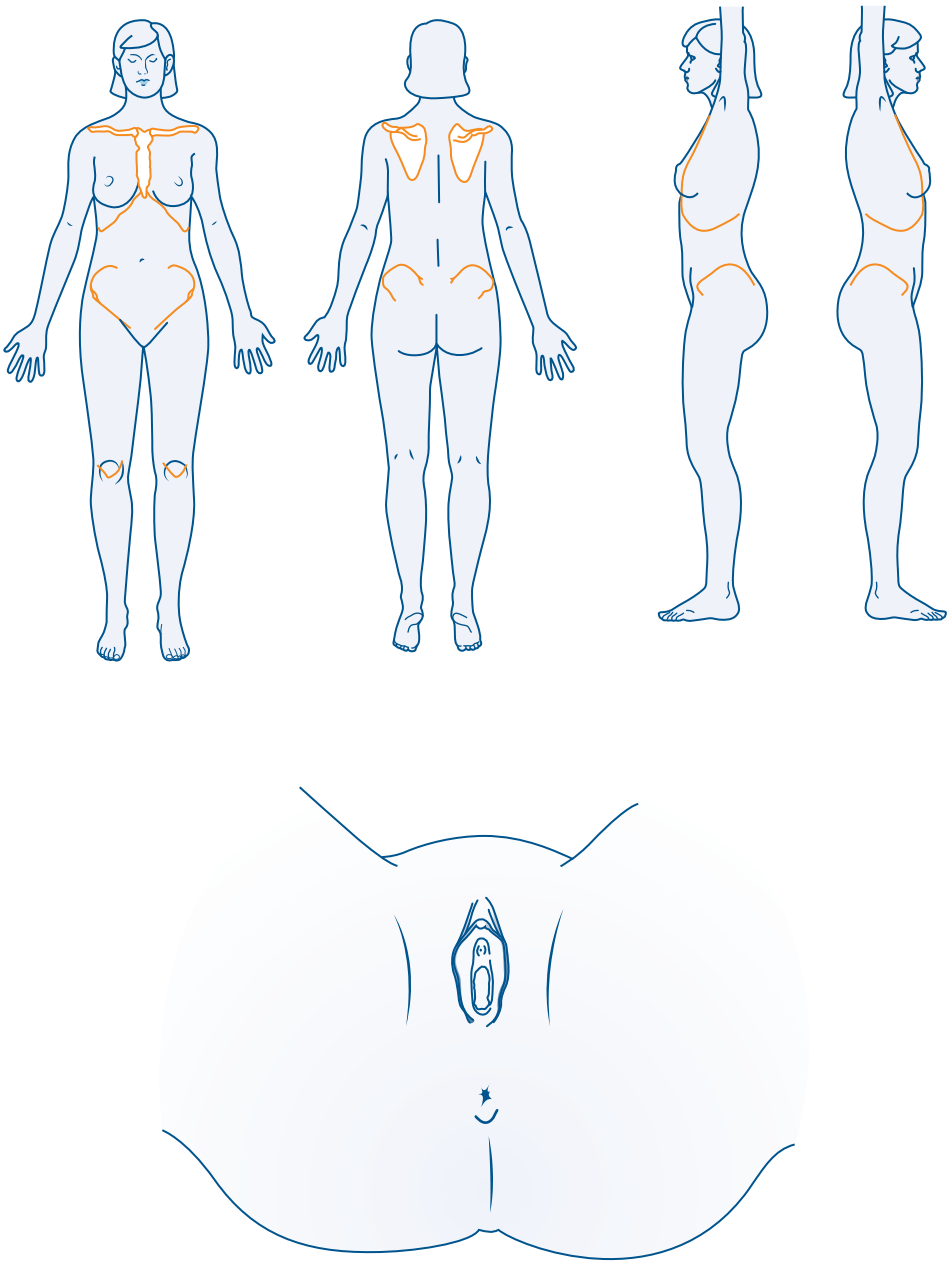

FIGURE 7.2 Chronic pelvic pain map. (From Howard F. Evaluation of chronic pelvic pain in women. UpToDate Web site. http://www.uptodate.com/contents/evaluation-of-chronic-pelvic-pain-in-women. Accessed November 25, 2013.)

of the pain. Asking these detailed questions will allow the clinician to deduce if the pain intensity is increasing despite relatively stable pathology.

In many instances, taking this type of complete history requires more than one visit. Once the clinician decides that he or she is dealing with a significant chronic pain problem, the patient should be prepared to attend several visits before the evaluation is complete.

The clinician needs to understand the impact the pain has had on the patient as an individual, on her relationships, and on her work capacities. The emotional components may be evaluated by the clinician's own history and possibly by psychometric evaluation or by psychological consultation. The purpose of psychometric instruments is to draw attention to particular problems, such as depression, that might not easily emerge from an interview. Their purpose is not to make psychiatric diagnoses; that responsibility remains with the clinician. Personality profiles can serve to define an individual's strengths and weaknesses but do not yield specific diagnoses. Taken as a whole, these instruments will convey to the patient your interest in knowing as much about her as possible before beginning treatment.

TABLE 7.1 Typical Pain Patterns and Descriptors

Pain Type	History	Physical Examination
Endometriosis	Gradual progression from dysmenorrhea to continuous pain Deep dyspareunia	Tenderness in implant areas
Pelvic congestion	Luteal phase increase Afternoon, evening increase Deep dyspareunia Relieved by lying down "Heavy," "aching"	BLQ and central pelvic pain Tender at ovarian points, broad ligaments
Levator spasm	"Falling out" pressure sensation Afternoon, evening increase Midvaginal dyspareunia Radiates to low back Minimal cyclicity Relieved by lying down	Tender to palpation increased by contraction
Piriformis spasm	Pain on arising, climbing stairs, driving car	Pain on external thigh rotation; palpated externally or transvaginally
Adhesions	Starts 3–6 mo after surgery Localized to adhesions pulling, tugging	Vague thickening Pain on visceral motion

BLQ, bilateral lower quadrant.
Reprinted from Steege JF. Office assessment of chronic pelvic pain. *Clin Obstet Gynecol.* 1997;40:554–563, with permission.

The clinician must also ask about past or present experiences with physical and/or sexual abuse. Many studies suggest that histories of abuse are more common in women referred to tertiary care specialty clinics for pelvic pain.[23] In the primary care setting, this association is also present, but it is substantially weaker.[24] In some cases, a history of abuse serves as a trigger for referral, whereas in others, referral is done only if the history is accompanied by complicated psychosocial problems. Women with histories of particularly traumatic or prolonged abuse may develop somatization disorder and/or posttraumatic stress disorder. These women may exhibit dissociative reactions during examination, appearing to have "drifted off," becoming withdrawn, and noncommunicative.[25]

Having obtained a history of sexual or physical abuse, the clinician is confronted with a dilemma: Is the abuse etiologically related to the person's pain? Or is it an unfortunate but unrelated aspect of her life? The full impact of physical and/or sexual abuse in an individual's history requires careful assessment. Great care must be taken that appropriate medical and surgical attention to organic disease is not undermined by overemphasis of a relationship between the patient's pain and her past history of trauma.

Physical Examination

The data provided by the history and observations made during the history taking process will provide focus for the physical examination. Before and during the history, the clinician may have the opportunity to observe posture, stance, gait, and sitting behavior. For example, a person with levator spasm will often sit forward on the chair and rest more of her weight on one buttock or the other. Sitting perfectly straight often aggravates the pain from this disorder.

The abdominal examination in a woman with CPP may be more informative if done in the following manner. Ask the patient to point to the area of pain with one finger and outline and circle the area involved. Ask her then to press as hard as she feels it is necessary in order to elicit the pain she experiences. Done in this manner, the impact of her anxiety about being examined may be diminished and a more accurate assessment of tissue sensitivity obtained. The patient is then asked to flex the abdominal muscles by raising only her head off the table and then asked to repeat the same palpation. If the pain elicited by palpation with the abdomen flexed is either the same or greater than the pain of the first palpation, then the abdominal wall itself is likely to be a source of the pain or a "pain generator." This is a positive Carnett sign. If pain from palpation of the tensed abdominal wall is less, then an internal visceral source(s) is more likely.

The abdominal wall should then be systematically palpated by the examiner's index finger in an effort to identify local spots of tenderness or "trigger points." A trigger point is a hyperirritable spot within a taut band of skeletal muscle fibers that is painful on compression and may give rise to referred pain, tenderness, tightness, and sometimes, local twitch response and autonomic phenomena.[26,27] A diagrammatic record of the examination findings is valuable.

Specific elements of the musculoskeletal examination should be performed to look for piriformis spasm and/or psoas muscle pain. The piriformis originates at the lateral margin of the sacrum, traverses the greater sciatic

notch, and inserts on the greater trochanter of the femur. Its function is to externally rotate the thigh. It also forms a muscular bed for the sacral plexus of nerves in the pelvis, and some or all of the sciatic nerve goes through the belly of the piriformis in 25% of women. With her hip and her knee partially flexed (i.e., in the stirrups), ask the patient to externally rotate each thigh in turn against resistance. Pain in the posterior hip area with this maneuver suggests piriformis spasm. Irritation of the sciatic nerve by this spasm can cause hyperreflexia and "pseudosciatica" or pain that mimics sciatic nerve compression seen in lumbosacral disc disease.

In the lateral decubitus position, the hip is actively and passively extended and flexed. Pain with these maneuvers suggests a psoas muscle origin. Further elements of the musculoskeletal screening examination are discussed elsewhere (Table 7.2).[23]

The pelvic examination in the patient with CPP is more informative when performed in a careful stepwise fashion. Meticulous attention is paid to each potential contributing organ system. While collecting this information, the examiner should be thinking of making a list of contributing factors, not examining until "the cause" of the pain is found. First, place one index finger in the vaginal introitus and ask for voluntary contraction and relaxation. Inability to exert conscious control of the bulbocavernosus muscles suggests vaginismus. This diagnosis should, of course, be corroborated by additional history. The presence of good voluntary control during pelvic examination does not exclude the diagnosis of vaginismus that may occur during sexual situations.[28]

Extending the index finger beyond the bulbocavernosus muscle, one can usually palpate the levator muscles on the right and left sides at approximately the 4:30 and 7:30 positions. In the asymptomatic person, a sense of pressure is experienced. When levator spasm is present, gentle palpation on these muscles may reproduce the patient's sense of pelvic pressure (a "falling out" sensation) and/or the pain of dyspareunia. Further verification is obtained when the symptom is exacerbated by voluntary contraction of the levators.

The next step is to press directly on the coccyx, reaching it with the vaginal finger by going around the rectum on either side. External palpation of the coccyx combined with this maneuver will normally allow it to flex and extend through an approximately 30-degree angle. This is normally not a painful maneuver. If pain is present, it may be related to coccydynia or adjacent levator spasm.

The piriformis muscle can be tested by the maneuvers described earlier. When these maneuvers suggest piriformis spasm, this can be further confirmed on pelvic examination. The belly of the piriformis can be easily felt transvaginally when the thigh is externally rotated against resistance. When palpation of the piriformis muscle belly reproduces pain, then spasm is likely to be present. A false-positive interpretation of this maneuver can occur if intrinsic cul de sac disease is present because the vaginal examination finger must traverse this area to reach the piriformis muscle (Fig. 7.3).

The anterior vaginal wall, urethra, and bladder trigone should be examined either before or after the muscular examinations just described, depending on the clinical situation. In general, it is best to examine the (likely) nontender areas first. This technique helps minimize the tendency to experience pressure as pain ("wind-up") once pain has been elicited. In many cases, the clinician can make the presumptive diagnosis of chronic urethritis, trigonitis, or interstitial cystitis on the basis of careful history combined with focused digital examination. If complex therapeutic interventions are being contemplated, then cystoscopic confirmation (i.e., cystoscopy with hydrodistention) should first be obtained. In the asymptomatic patient, pressure on the bladder base creates only urinary urgency without replicating the clinical pain.

Unimanual, single-digit transvaginal examination should continue by testing the intrinsic sensitivity of the cervix to palpation and traction. The adnexal areas are then examined in a similar manner, first unimanually and then adding the abdominal hand. Separating the pelvic exam into three discrete steps (unimanual vaginal exam alone, unimanual external exam of lower abdomen alone, and then examining the pelvis bimanually) helps distinguish internal visceral pain from pain originating from the abdominal wall.

Rather than following a rigid sequence, speculum examination should be done at a time when it makes the most sense, depending on the type of pain under consideration. For example, in the patient with a history suggesting posthysterectomy vaginal apex pain, it is probably wisest to complete the muscular examination as well as the adnexal palpation *prior* to insertion of the speculum. In this manner, the areas more likely to be

TABLE 7.2 Musculoskeletal Screening Examination for Chronic Pelvic Pain

Observation/Maneuver	Typical Abnormal Findings
Gait, stance	Scoliosis
Lateral standing view	One extremity externally rotated; exaggerated kyphosis-lordosis
Sitting	Raised up on one buttock (levator spasm)
With supine flexion of one hip, observe other hip (Thomas test)	Contralateral hip flexes, indicating hip flexor contracture
External rotation of the thigh against resistance (sitting, supine, or during pelvic examination)	Pain on external rotation indicates piriformis syndrome
Psoas flexion and extension	Limited extension and/or pain with flexion indicates psoas shortening ± spasm
Digital vaginal examination	Pain indicates levator spasm

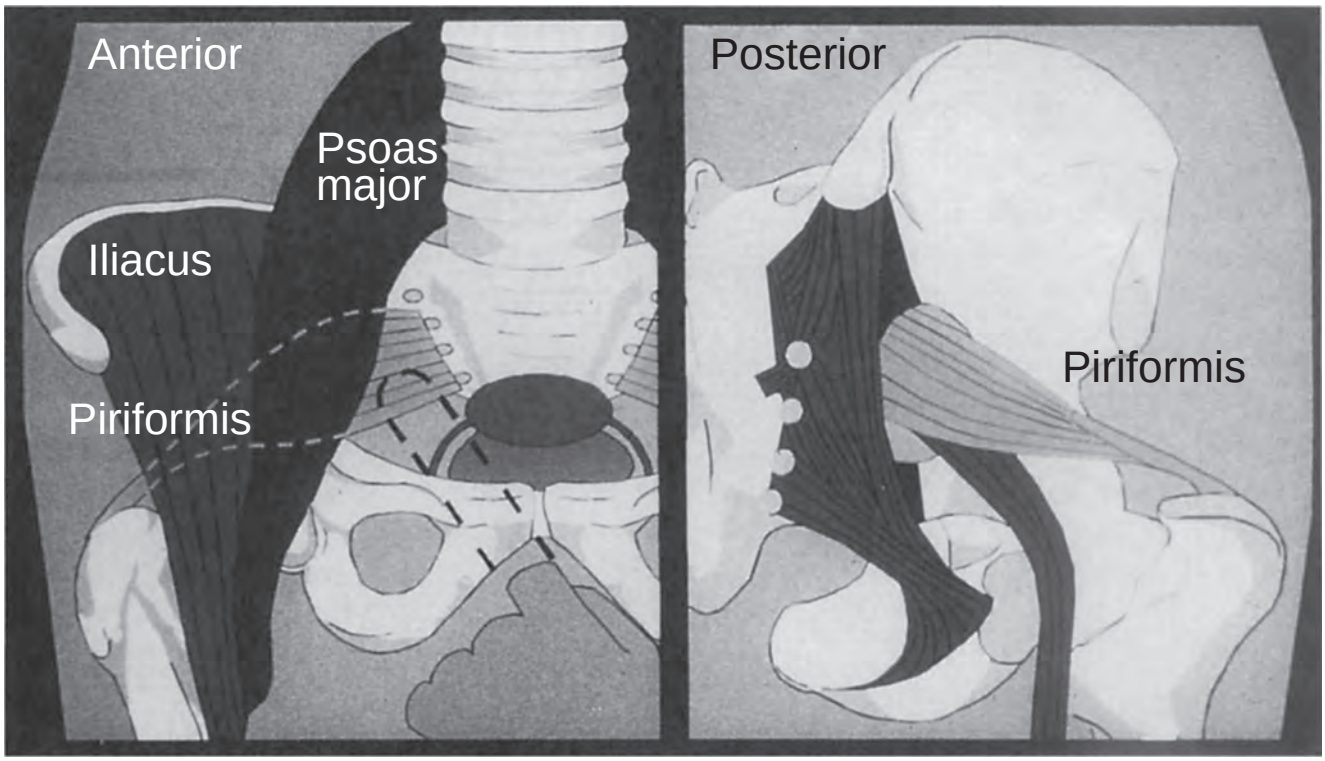

FIGURE 7.3 Vaginal examination of piriformis muscle. (Modified from Barton PM. Piriformis syndrome: a rational approach to management. *Pain*. 1991; 47[3]:345–352.)

nontender are examined prior to the speculum directly touching the potentially sensitive vaginal apex.

In contrast, if the history suggests an adnexal source of pain, then the pelvic examination should begin with the speculum examination (as is traditionally done). The speculum examination is then followed by a pelvic musculoskeletal exam, leaving the adnexal examination for last. To determine if adnexal pathology exists to a sufficient degree to contribute to the pain, the examiner need only palpate with a single vaginal finger. This avoids confusing the diagnostic picture by using the traditional bimanual exam, which may mingle pain signals from the abdominal wall with those from the adnexa. The gynecologist, focusing on the reproductive organs, may interpret all pain as coming from this system, sometimes leading to overtreatment of the adnexa. Having examined the adnexa for pain with the single-digit exam, the traditional bimanual adnexal exam can then evaluate size, shape, and mobility. Throughout each portion of the examination, the clinician should ask whether any tenderness elicited reproduces the pain of her chief complaint.

Rectovaginal examination remains an essential component of the complete pelvic exam, especially in the case of pain noted with defecation (dyschezia). Insertion of the rectal finger causes the least discomfort if the middle finger is placed gently at the anus and exerts slow, gentle pressure in a dorsal direction. Some clinicians are taught that having the woman bear down will facilitate insertion of the finger. When most patients "bear down," however, they do a Valsalva maneuver and simultaneously contract the voluntary portion of the anal sphincter. This causes an increase in discomfort and makes digital insertion more difficult. The rectal finger should advance as far as possible, ideally reaching the hollow of the sacrum. In this manner, the entire floor of the posterior cul de sac can be thoroughly evaluated for the presence of irregularities or nodularity that might imply the presence of deep infiltrating endometriosis (DIE). To fully evaluate the uterosacral ligaments, a rectovaginal examination is done. The uterosacral ligaments can be more accurately assessed by putting the cervix on traction in an anterior direction with the tip of the vaginal finger while palpating the stretched uterosacral ligaments with the rectal finger.

After palpation of the uterosacral ligaments, the bimanual portion of the examination is repeated with sequential palpation with the rectovaginal hand, the abdominal hand, and both hands together. When examining areas that are tender, it is useful to pause and inform the patient that examination of the tender area will only last for a count of "one, two, three . . ." and will only begin when she feels ready. By time limiting this portion of the exam and allowing the woman to determine when it will commence, the examination is made more tolerable for the patient. When tenderness is elicited,

the clinician should ask whether this reproduces the clinical pain the patient is experiencing.

Office Diagnostic Procedures

Trigger point injections have been well established as a diagnostic and therapeutic technique.[29,30] The trigger point is identified first through palpation and then with the needle before injection. Eliciting the local twitch response, a brisk contraction of the taut band (but not the surrounding normal muscle fibers), is essential for success.[31–33] Multiple types of local anesthetics (e.g., 1% lidocaine or 0.25% bupivacaine) have been used with none demonstrably superior to any other. The pain of injection can be substantially reduced by adding sodium bicarbonate (1 mL per 10 mL of 1% lidocaine; 0.2 mL per 30 mL of 0.25% bupivacaine). A 27-gauge tuberculin needle or a 25-gauge, 1.5-in. needle is preferable for injection. The use of botulinum toxin A is appealing for chronic myofascial pain for its local, temporary muscle paralysis and its reduction of neurogenic inflammatory mediators. The effects from botulinum toxin injections may last between 3 and 6 months, although it is costly therapy. If the abdominal wall trigger points can be blocked successfully, then the pelvic examination might then be repeated in order to better understand the contributions of intrapelvic pathology to the patient's pain.

Similarly, local injection can be used to anesthetize the vaginal apex tissue in an effort to determine whether this tissue is intrinsically sensitive, or whether pain elicited from vaginal cuff palpation on bimanual examination emanates from intrapelvic pathology.

Transvaginal ultrasound examination provides very useful information in evaluating acute pelvic pain. Unfortunately, it is less contributory for the evaluation of CPP complaints. The occasional exceptions to this generalization will be noted as individual pelvic pain syndromes are discussed in the following section.

SPECIFIC PELVIC PAIN SYNDROMES

Endometriosis

Certain historical stigmata signal the possibility that endometriosis may be present. Severe dysmenorrhea during adolescence with worsening in early adult life should suggest this etiology. With endometriosis, the duration of severe dysmenorrhea may also change. In cases of primary dysmenorrhea not due to endometriosis, the typical pattern is for the first day of menses to be the most painful. This is followed by a roughly 50% reduction in pain on the second menstrual day. If endometriosis develops, the duration of the more severe menstrual cramps may lengthen and the severe dysmenorrhea may last into the second or third menstrual days. The next change may be the appearance of premenstrual pain, ultimately followed by pain present for almost all of the menstrual month but with continuing premenstrual and menstrual exacerbations. Deep dyspareunia may join the picture at any point along the way, usually appearing perimenstrually at first.

Early in the disease of endometriosis, physical examination may not detect any abnormalities, but when endometriosis is at a stage where deep dyspareunia and severe dysmenorrhea are present, the examination may reveal focal cul de sac tenderness and nodularity of the uterosacral ligaments. Increased attention has been paid recently to DIE in the cul de sac of Douglas, which may not be readily visualized during laparoscopy.[34,35] The chances of detecting palpable nodularity may be increased by examining the patient during menstruation. At this point, the nodularity may be more palpable as well as more tender.

It is now generally accepted that there is more than one subtype of endometriosis.[35] In addition to DIE, there are two common varieties of endometriosis: one with multiple peritoneal implants, predominantly in the cul de sac or on the ovaries, and a second variety appearing primarily as intraovarian disease or endometriomas. The intraovarian variety is not frequently associated with dysmenorrhea and pelvic pain and is often diagnosed by an incidental finding of ovarian enlargement. Pain may appear if the endometrioma(s) become quite large.

The deep infiltrative variety, quite distinct from the other two, consists primarily of posterior deep cul de sac disease. Laparoscopy in such cases may reveal only the mildest signs of peritoneal abnormality, with the bulk of the disease hidden in the retroperitoneal space next to the rectum and at the vaginal apex. This last variety has been called vaginal adenomyosis by some authors.[36] It has been described as being potentially due to a Müllerian anomaly rather than resulting from retrograde menstruation (Sampson theory). Diagnosis of deep, infiltrating cul de sac endometriosis can be quite difficult. Transvaginal ultrasound, in experienced hands, can be quite sensitive and specific in detecting bowel endometriosis in this area, and transrectal ultrasound has been used as well. Special magnetic resonance imaging (MRI) techniques may be done as well, but this area is acknowledged to be difficult to interpret on MRI. During laparoscopy, detection of deep disease is enhanced by performing rectovaginal examination with one hand while using the other to maneuver a smooth, 5-mm laparoscopic probe into the posterior cul de sac area. The tissues of the area can be palpated between the rectovaginal fingers and the probe, offering a very sensitive means of detecting lesions as small as 2 to 3 mm. Treatment is thought to be primarily surgical because sex steroid receptors are reduced in this type of disease when compared to more typical peritoneal disease.[37]

Other physical findings of endometriosis may include a fixed, retroverted uterus as well as generalized pelvic

tenderness. Differentiating this diagnosis from chronic pelvic inflammatory disease (PID) or other forms of pelvic masses may be difficult.

With the possible exception of new approaches using MRI techniques, imaging studies in general are not very useful in the diagnosis of endometriosis. Transvaginal ultrasound may detect cystic enlargement of the ovaries, but endometriomas may have a variety of different ultrasonic appearances, none of which are unique to this disorder.

Medical management of this disorder most reasonably starts with cyclic oral contraceptives. Continuous oral contraceptives may be employed as well, thus avoiding the discomforts of regular menstruation. To go beyond this first order of therapy is to ask the patient to incur significantly greater expense, side effects, and disruption of her normal endocrinologic milieu. For these reasons, most authorities advocate laparoscopic confirmation of the diagnosis prior to embarking on more intrusive medical therapies such as danazol (Danocrine), continuous high-dose progestins, or gonadotropin-releasing hormone (GnRH) agonists (Table 7.3).

One study has challenged this traditional view. Ling[30] tested the ability of clinicians to diagnose endometriosis on clinical grounds without laparoscopy. In 95 women, 82% were found to have visual evidence of endometriosis at the time of laparoscopy (biopsy for proof by pathology was not uniformly done). Prior to this surgery, they had been randomly assigned to treatment with leuprolide or placebo. The active drug relieved pelvic pain with equal frequency in women with or without endometriosis. This means that pain relief on leuprolide did not make the diagnosis of endometriosis; laparoscopy was still required. (The American Society for Reproductive Medicine supports this stance.) Unfortunately, the study has been widely misinterpreted to mean that when pain goes away on leuprolide, endometriosis is present.

Until recently, surgical treatment of minimal and mild endometriosis by laparoscopic methods was thought to be equivalent to medical management in improving fertility. However, a randomized trial demonstrated a more rapid accomplishment of the desired pregnancy following laparoscopic treatment of the disorder when compared to expectant therapy.[38] Similar comparisons of medical and surgical treatments of endometriosis for the purpose of pain relief have not been performed.

Various opinions exist about the appropriate technique for laparoscopic treatment of endometriosis. Electrocoagulation or laser treatment of superficial implants is regarded as sufficient for very small foci of disease. When confluent collections of implants are noted or when active red or purple lesions are found, some surgeons prefer laser vaporization for definitive therapy. Others believe that excision of the entire area of involved peritoneum is the only way to adequately remove the disease to its depths.[39] When extensive areas of peritoneum are removed, however, severe peritoneal adhesions may be the sequelae. This may result in trading endometriosis for adhesive disease as the pain etiology.

Women dealing with endometriosis may also develop some of the other chronic pain syndromes described in the following sections, such as pelvic congestion, musculoskeletal problems, and/or irritable bowel syndrome. Careful attention to the nature and chronology of symptoms will usually allow separate consideration and treatment of these disorders.

Recent investigations have focused on the phenomenon of neurovascular invasion of endometriosis implants as playing a role in pain production. Using the neuroinflammatory mechanisms mentioned above, the development of centralized/neuropathic pain may ensue, making the endometriosis implants themselves much less relevant.[40] This may account for the common observation of return of pain following surgical treatment of endometriosis but then finding very little recurrent disease when laparoscopy is repeated. Accurate assessment of this process is further hindered by the ability of surgery to have a nonspecific effect on a high percentage of patients that lasts a long time, up to a year or more. When the pain returns a year after surgery, is it return of the endometriosis or the wearing off of the placebo effect of surgery?

TABLE 7.3 Medications Used in Conjunction With Gonadotropin-Releasing Hormone Agonists

Norethindrone	Estrogen + progestin (continuous)
Etidronate	Estrogen + progestin (cyclic)
Norethindrone + etidronate	Calcitonin
Estrogen (oral and transdermal)	Calcium
	Medroxyprogesterone acetate

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Postpelvic Inflammatory Disease

Up to 30% of women will develop CPP after PID. Two factors appear to be related to the likelihood of this: the severity of tubal damage and adhesion formation and the continuation of pelvic tenderness 30 days after the diagnosis and treatment.[41] The mechanisms for this association between PID and CPP are not fully understood at this time.

Pelvic Adhesions

Intra-abdominal adhesions are found in approximately 30% of autopsied women older than 60 years of age.[42]

In asymptomatic women undergoing laparoscopic tubal sterilization, adhesions are found in approximately 12% of the women.[43] Among women undergoing laparoscopy for CPP, adhesions are found between 45 and 90% of the time.[44]

Studies of the impact of adhesiolysis on CPP have been relatively limited. Uncontrolled series suggest that 65 to 85% of treated women obtained significant relief 8 to 12 months after surgery.[45,46] One randomized trial showed adhesiolysis by laparotomy to be superior to diagnostic laparoscopy only in the small percentage of women with dense bowel adhesions.[47] This latter study did not evaluate the impact of the laparoscopic approach to adhesiolysis.

These results suggest that certain types of adhesions may play an etiologic role in CPP, but by no means are they always responsible for pain generation. The clinician is left with the challenge of providing a balanced interpretation of the role of adhesions in pain causation and the role of adhesiolysis in the overall pain management plan.

The clinical diagnosis of adhesions is quite difficult. It is possible to assess the relative mobility of the pelvic viscera during examination, but adhesions can only be strongly suspected when they are quite extensive. Transvaginal ultrasound is another way to evaluate the mobility of the pelvic organs, but it has low sensitivity and specificity in predicting the presence of adhesions. Sophisticated imaging studies, such as computed tomography (CT) scans and MRI, are ineffective in diagnosing adhesions; the gold standard for diagnosing adhesive disease remains diagnostic laparoscopy.

Following laparoscopic adhesiolysis, adhesions will start to reform within 1 to 2 weeks after surgery. Pain may not recur for another several months. The mechanism of this delay is uncertain, but strong possibilities include the time necessary for adhesive tissue to become well collagenized and contract, as well as the time required for neural ingrowth. The overall prevalence of nerve tissue in adhesions is uncertain, as is its role in pain generation.

In summary, treatment of adhesions in some cases may play an important role in the management of CPP. In many situations, it is wisest to simultaneously direct treatment efforts to other visceral and somatic sources of the pain as well as to the affective components in order to bring about the best resolution.

Adenomyosis

Adenomyosis is a condition in which endometrial glands and stroma grow within the myometrium, usually without direct connection to the endometrium. For true pathologic diagnosis, these glands and stroma must be present three high-powered fields below the basal layer of the endometrium. Adenomyosis is an extremely common condition, generally thought to be present in parous women in their 30s and 40s. Its relationship to symptoms is uncertain because it may be present in as many as 30% of women, most of whom are asymptomatic.[48] Its role as a post hoc justification for hysterectomy in a woman with an otherwise anatomically normal pelvis has made it the focus of significant controversy.

Traditionally, the diagnosis has only been possible by histologic examination of the uterine wall. Transvaginal ultrasound, MRI scanning, and myometrial needle biopsy have all been employed in an effort to make a preoperative diagnosis. Although these efforts are encouraging, they lack sufficient resolution and standardized criteria and technique to explain or quantify the pathophysiologic process or relationship between histologic changes and clinical symptoms.

On a clinical basis, it may be useful to use serial pelvic examinations, possibly in combination with transvaginal ultrasound, in evaluating the potential role for adenomyosis as the etiologic source of the woman's pelvic pain. A woman who has a truly substantial amount of this disease will often demonstrate substantial cyclic changes in the size, consistency, and tenderness of the uterine fundus. In the follicular phase, the uterus will be smaller and firmer, whereas immediately premenstrually it will be enlarged as much as 1.5-fold over its baseline and will be extremely tender and much softer in consistency.

Pharmacologic therapy has been attempted with continuous oral contraceptives, luteal phase progestins, danazol (Danocrine), or GnRH agonists. Although success has not been confirmed by clinical trials, there are patients who report that luteal phase medroxyprogesterone acetate (Provera) provides sufficient reduction of pain as well as diminution of menometrorrhagia. The Mirena intrauterine device (IUD) may also be efficacious in some cases. When any of these therapies are successful, the clinician must decide whether their long-term use makes practical and clinical sense.

Whether hysterectomy is appropriate for this condition is a matter of considerable debate, especially in the current era of managed care. The condition is not life-threatening, and when medical therapy works, the discussion of further surgery centers primarily around quality of life issues. In this case, as in many others, the discussion of medical necessity leaves off, and the discussion of personal preferences and cultural expectations begins.

Pelvic Congestion

Over the past 60 years, this syndrome (and its many different names) has been widely described in the literature. Discomfort has been associated with distention of abnormal pelvic veins. In the early literature, a variety of other pathologic findings were attributed to the process.[49,50] More recent studies indicate the venous distention itself is primarily responsible for the production of symptoms.[51,52] A recent thorough review of the available literature concluded that the syndrome itself

has not been rigorously defined and speculated that it has largely been used as a diagnosis of exclusion.[53] The present author's experience is that it is rarely diagnosed in his clinical practice. What follows is a review of some older literature because relatively little of value has been published in recent years.

As much or more than any other gynecologic disorders related to pain, it is in this instance that mind–body interactions have been most intensely debated. Early publications by Taylor described a population of women with enlarged pelvic veins who had otherwise normal pelvic anatomy but whose psychosocial histories divulged a high prevalence of early deprivation and abuse. He described increases in vascular pelvic congestion (measured by increases in vaginal blood flow detected photometrically) that occurred only during interviews dealing with stressful topics.[51,52] Using similar methodology, however, a later investigator described the same phenomenon in pain-free controls.[54]

Documentation of pelvic varices has been primarily demonstrated by transuterine venography.[55] In this procedure, radiopaque aqueous contrast material is injected into the uterine fundus transvaginally, and x-rays are taken at closely spaced intervals to document the passage of this contrast through the pelvic veins. Scoring criteria have been developed.[56]

The symptom pattern associated with this disorder includes a sensation of pressure low in the pelvis that worsens during the course of the day and premenstrually, deep dyspareunia, and a subset of women who experience menorrhagia. Bladder irritability and altered bowel habits are also found in some series, thus confusing the diagnostic picture.[49,50] Its prevalence is uncertain because reports from experts on pelvic congestion may reflect a higher incidence than what is true for the general population.[49,50] Given the complexity of this disorder, prescription and assessment of therapeutic measures must be done carefully.

Concrete physical examination findings in this disorder are limited. Beard places emphasis on the detection of pain at the "ovarian point."[50] This is located two-thirds of the way from the anterior superior iliac spine to the umbilicus. Tenderness in this area may be present in women without other evidence of this disorder and therefore this sign may not be consistently diagnostic. Bimanual examination will reveal a "doughy" consistency to the parametrial areas, and the patient will report these areas as the most sensitive areas in the pelvis. Examination in the premenstrual period may demonstrate substantial change in consistency of this area when compared with a follicular phase examination.

Diagnostic laparoscopy will often miss this diagnosis. Laparoscopy is usually performed early in the day with the patient in Trendelenburg position. Attempts have been made to examine the pelvis laparoscopically with the patient in reverse Trendelenburg position using a volume of irrigating fluid to float the bowels out of the way. This approach has not been systematically studied or validated. Diagnostic ultrasound is being evaluated for this disorder, but the technique has been difficult to standardize.[57]

Pelvic congestion has been treated by suppressing the menstrual cycle. One study using GnRH agonists with estrogen and progestin add-back therapy did not demonstrate relief.[58] Oral contraceptives have been similarly ineffective.[59] In contrast, continuous high-dose medroxyprogesterone acetate (Provera) (30 mg daily) in combination with a six-session course of psychotherapy has produced a minimum of 50% improvement in three-quarters of the women in one study.[60] The psychotherapy focused on stress management and establishment of a better understanding of mind–body interactions. Medroxyprogesterone acetate (Provera) alone showed similar benefits when compared with placebo, but the duration of the effect was much greater when medical therapy was combined with counseling.

Surgical therapy has traditionally involved hysterectomy.[61] In the most severe cases, bilateral salpingo-oophorectomy is also recommended. Less radical approaches have included ligation of individual varices, although this has proven relatively unsuccessful. Other techniques are individual ovarian vein ligation or ligation of the entire infundibular pelvic ligament, with the literature describing a modest effect from this latter approach.[62]

Although surgical therapy or intense medical therapy remain the mainstays of treatment, pharmacologic therapy with progestins and behavioral methods of stress reduction are central to an effective treatment plan.

Irritable Bowel Syndrome

The symptoms of irritable bowel syndrome (IBS), also called visceral hyperalgesia, are frequently misinterpreted as being of gynecologic origin. In primary care populations with CPP, IBS is one of the most common diagnoses and may occur in up to 35% of these women; unfortunately, for many women with both CPP and IBS, the IBS is neither diagnosed nor treated.[63,64]

The International Consensus Criteria require that abdominal pain be relieved by defecation or associated with a change in the frequency or consistency of stools; in addition, two or more of the following symptoms must be present:

1. Altered stool frequency
2. Altered stool form
3. Dyschezia or urgency
4. Passage of mucus
5. Bloating[52]

Alternative etiologies can be ruled out with flexible sigmoidoscopy, stool guaiac testing, and hematologic tests that screen for immunologic problems or thyroid dysfunction. A recent stool test looks for white blood cell products that are excreted in the presence of inflammatory bowel disease (IBD).

TABLE 7.4 Differential Diagnosis of Painful Gastrointestinal Disorders That May Present as Pelvic Pain

Disorder	Symptoms	Diagnostic Test
Lactose intolerance test	Cramping pain, flatulence after milk products	Lactose tolerance
Small bowel bacterial overgrowth and diarrhea growth	Postprandial bloating	Hydrogen breath test
Chronic intestinal pseudo-obstruction	Migratory abdominal pain	Small bowel motility study
Inflammatory bowel disease	Copious diarrhea, sometimes bloody	Endoscopy, x-ray contrast studies
Diverticulosis	Pain, diarrhea	Endoscopy, contrast studies
Bowel endometriosis	Pain with bowel movements, ± alteration of bowel function	Endoscopy, laparoscopy

The differential diagnosis includes lactose intolerance, bacterial overgrowth of the small intestine, chronic intestinal pseudo-obstruction, IBD, diverticular disease, levator ani syndrome (proctalgia fugax), and/or endometriosis affecting the bowel (Table 7.4).

There appears to be a fairly strong association of IBS with dysmenorrhea.[65] IBS is more common in women who have undergone hysterectomy in the absence of identifiable gynecologic pathology compared to women who underwent hysterectomy for pathology.[66] IBD such as Crohn disease or ulcerative colitis is a concern as well. About a third of women with IBD will also fulfill the Rome criteria for IBS.[67] Fecal calprotectin is a new screening test for IBD that is up to 90% sensitive and 80% specific for that disorder.

In rectal manometric studies, approximately 40 to 60% of IBS patients report pain at levels of distention below the range of normal values.[68] Although controversial, this observation may serve as a marker for IBS when combined with other clinical indicators. This lowered pain threshold may reflect a difference in the sensitivity of peripheral stretch receptors or pain afferent pathways. Attempts have been made to correlate these physiologic observations with measures of psychological stress or affective change, with mixed results.[68,69] In addition to the "visceral hyperalgesia" phenomenon suggested by these studies, IBS patients may have increased colonic motility and have abnormal small bowel motility as well.[70,71] None of these physiologic markers is specific enough to be used as a single diagnostic sign of IBS. Fifty to 85% of patients with IBS report that psychological stress exacerbates their bowel symptoms.[69] One study found that 53% of women with IBS referred to tertiary care centers had a history of previous sexual abuse compared to 37% of those referred with other organic diagnoses. This same pattern is not seen at a primary care level.[72]

The medical management choices for IBS are dictated by the predominant symptom(s) (Table 7.5). If diarrhea is the major symptom, a variety of antispasmodic medications such as diphenoxylate (Lomotil), hyoscyamine (Levsin, Donnatal), and dicyclomine (Bentyl) are used. Desipramine (Norpramin) or other tricyclic antidepressants are also effective, and they have the added benefit of treating the chronic pain syndrome component of the problem.

Constipation is best treated by increased fiber and water intake. Lactose and sorbitol are effective but increase abdominal bloating. A very effective but more expensive treatment is cisapride (Propulsid), although it may manifest side effects of dizziness and headaches.

For general pain treatment, the serotonin reuptake inhibitors have not been widely explored, although one study suggests that 5HT3 receptor antagonists (such as granisetron HCl [Kytril]) will lower the increased pain sensitivity seen in IBS patients.[73]

Psychological treatments for IBS have included relaxation training, cognitive behavioral therapy, hypnosis, and individual psychotherapy. Each of these modalities

TABLE 7.5 Pharmacologic Treatment of Irritable Bowel Syndrome

Symptom	Drug	Daily Dose	Major Side Effects
Diarrhea	Loperamide (Imodium)	Titrate; 4 mg average	Constipation
	Diphenoxylate HCl	20 mg	Euphoria, sedation, dry mouth, constipation
	Hyoscyamine sulfate (Levsin, Donnatal)	<1.5 mg	Dry mouth, blurred vision, dizziness
	Dicyclomine HCl (Bentyl)	80–160 mg	Dry mouth, blurred vision, dizziness
	Desipramine HCl (Norpramin)	150 mg	Dry mouth, sedation, confusional states, hypertension, hypotension, constipation
	Trimipramine maleate (Surmontil)	50 mg	Dry mouth, sedation, confusional states, hypertension, hypotension, constipation
Constipation	Fiber from any source	≥30 g	Bloating, abdominal pain
	Lactuiose (Chronulac, Duphalac)	10–30 g	Bloating
	Sorbitol	10–30 g	Bloating
	Cisapride (Propulsid)	40–80 mg	Dizziness, headaches

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has research studies that support efficacy, and some studies have used them in one or more combinations.[74,75]

As a matter of practicality, the first-line approach for severe IBS includes dietary change, increased fiber and water intake, an anticholinergic for diarrhea-predominant patients, and tricyclic antidepressants when pain is the major complaint. If these interventions fail, mental health referral should be considered.

Musculoskeletal Problems

Painful spasms of the pelvic floor and hip muscles are frequent components of CPP. On occasion, a woman may develop, for example, piriformis spasm as a result of athletic injury, and the problem may be misdiagnosed as gynecologic in nature. Far more commonly, in response to a prolonged problem originating from the reproductive, gastrointestinal (GI), or urinary tract viscera, these muscle groups may individually or collectively become dysfunctional. They therefore may continue as pain generators even after the initiating visceral problem has been resolved.

Myofascial pelvic pain syndrome is used when there is pelvic pain and the pelvic floor muscles are short, tight, and tender. Abdominal and pelvic myofascial pain and trigger points are seen in many patients with CPP. Rigorous clinical trials for the most effective treatment of myofascial pain syndrome are lacking, but there is some evidence that treatment by a physical therapist (PT) or physician trained in musculoskeletal disorders in women's health care is ideal and myofascial physical therapy may be helpful.[76,77] Heat may also be useful for myofascial pain. There does appear to be some correlation between visceral inflammation and myofascial abnormalities in tissues that share the same innervation.[78]

Levator Ani Spasm

Spasm of the levator ani muscle(s) is perhaps one of the most frequently overlooked findings in the patient with pelvic pain. Historically, the person will describe a sensation of her pelvis "falling out," which is worse later in the day. The pain commonly radiates to the lower back or sacral area and may increase premenstrually. This premenstrual increase is less dramatic than that seen with endometriosis or pelvic congestion. The spasm may be relieved by lying down and is aggravated by defecation. Pelvic examination reveals tenderness specific to the levator muscles. This is most readily elicited by vaginal palpation of the pelvic floor in the "4:30" and "7:30" directions with the index finger. In order to amplify the finding, ask for voluntary contraction of the pelvic floor, such as what might occur during attempts to hold back defecation. The patient should then be asked how closely any discomfort mimics her chief complaint.

In this setting, it may be helpful to teach pelvic floor muscle relaxation exercises. The patient is asked to tighten the pelvic floor for a count of "one" or "two" and relax for a count of "seven" or "eight." In essence, these are "reverse" Kegel exercises. The patient is counseled that when she is standing and notes this sense of pelvic pressure, if she simply lets it "fall out," this will relax the pelvic floor.

In the past 10 years, an entire subspecialty has developed in the world of physical therapy that deals with muscle contributors to pelvic pain (pelvic floor physical therapy). There are many PTs who have taken extensive training in transvaginal work on the pelvic floor and hip muscles to the great benefit of many women. It is important to find an experienced pelvic floor PT, so that internal vaginal release work is done in conjunction with external soft tissue manipulations and trigger point release(s). There is some evidence that the duration of symptoms prior to therapy may correlate with the time it takes for therapy to aid in resolution of symptoms, and period follow-up sessions for pain flares may be needed.[79]

Piriformis Muscle Spasm

The piriformis muscle originates in the lateral margin of the sacrum and pass through the greater sciatic notch to attach to the greater trochanter of the femur. Its function is to assist in external rotation of the thigh. When this muscle is in spasm, the patient may notice pain upon first arising and starting to walk, with climbing stairs, or with driving a car. The pain is present regardless of time of day and phase of the menstrual cycle.

Upon physical examination, the pain is elicited by (a) externally rotating the entire leg in the supine position or (b) externally rotating the thigh against resistance while transvaginally palpating the piriformis muscle during this maneuver. When cul de sac pathology is present, the transvaginal palpation of the piriformis may yield a false-positive result. In addition to being associated with initial gynecologic problems, piriformis syndrome may develop as a result of athletic injury or as other inflammatory conditions such as trochanteric bursitis. As a normal anatomic variant, the sciatic nerve may traverse the belly of the piriformis in up to 20 to 30% of people. With this anatomic variant, when the piriformis goes into spasm, pseudosciatic symptoms may appear.

Treatment for the piriformis syndrome involves range of motion exercises, heat, local massage, deep ultrasound, and other physical therapy techniques. Continuous nonsteroidal anti-inflammatory drugs are useful as well and should perhaps be a first-line agent.

Additional musculoskeletal dysfunctions that may develop as a response to initial gynecologic problems may include shortening and spasm of the psoas, shortening

of the abdominal muscles, and/or a general abnormal posture including increased lumbar lordosis and an anterior tilt of the pelvis. The original gynecologic problem may promote splinting or cessation of exercise, leading to muscle(s) of abnormal lengths, that is, longer or shorter. This may induce tissue damage that results in the development of trigger points. Injection therapy for trigger points may not yield long-term results unless they are supplemented by physical therapy techniques aimed at re-establishing normal posture, muscle length, and muscular relaxation.

The musculoskeletal disorders listed previously as well as others may develop primarily and not in response to other pain etiologies. When these problems are detected coincidentally with known gynecologic pathology, clinical judgment as to which component is the more likely originator of the pain disorder is difficult.

Urinary Tract Disorders

Problems of the bladder and urethra may be roughly grouped as anatomic, inflammatory, or functional. Although anatomic or structural urologic causes of CPP occur, the majority are either inflammatory or functional in nature.

Problems resulting from pelvic relaxation are the most common structural disorders of the urinary tract. A pronounced cystocele may result in urinary retention and chronic, recurrent urinary tract infection. Ordinarily, the history and physical examination readily detects this anatomic problem. Postcoital antibiosis and voiding and, at times, daily antibiotic prophylaxis will treat most cases of chronic infection. When possible, surgical repair of the cystocele is most appropriate.

A urethral diverticulum is a relatively infrequent cause of pelvic pain. A bulging mass underneath the urethra may be appreciated, although in many cases, urethroscopy and/or a urethrogram with a double balloon Davis catheter is needed. By history, the patient may report dribbling when she stands up after voiding. On examination, even if a bulge cannot be appreciated, an area of focal tenderness along the course of the urethra may be palpable.

Perhaps the largest overall category of bladder problems contributing to CPP is the inflammatory disorders. Chronic, recurrent urinary tract infection is perhaps the most common, followed by chronic, bacterial urethritis. In the latter disorder, clean catch urine cultures may yield colony counts significantly less than 100,000 CFU/mL and are erroneously reported as "negative." Diagnosis can be made by historical reports of urethral pain as well as generalized tenderness to palpation along the entire urethra. A short course of antibiotics may help symptoms subside, but prolonged courses of 3 months or more are often needed to produce long-term relief. Urethral dilation is an outmoded treatment for chronic urinary tract infection but may have occasional application in refractory cases of chronic urethritis.

Much attention has been focused on the very difficult problem of interstitial cystitis. This disorder typically presents as frequency, nocturia, urgency, and suprapubic pain, often relieved by voiding. Dyspareunia is present in as many as 60% of female patients. The disorder may present in a mild, intermittent form initially but may gradually progress to a more chronic and disabling pattern over several years.

The diagnosis of interstitial cystitis is made by cystoscopy and hydrodistention under general or regional anesthesia.[65] The bladder is distended to 80 cm of water pressure with gravity filling over a period of 1 to 2 minutes, noting final bladder capacity. Typically, total bladder capacity during anesthesia is reduced from a normal value of 800 to 350 mL or below. The bladder is then emptied and refilled. At this point, the cystoscope typically reveals glomerulations that look like small petechiae, or submucosal hemorrhages, fissures, and/or ulcers. Quantitatively, the diagnosis is made when these lesions appear in at least three quadrants of the bladder with at least 10 glomerulations per quadrant. Bladder biopsy may be done to rule out other diseases such as eosinophilia, cystitis, endometriosis, chronic cystitis, and carcinoma in situ. The hydrodistention process itself may reduce symptoms in 30 to 60% of patients. Although a positive cystoscopy-hydrodistention makes the diagnosis of interstitial cystitis, debate surrounds the question of whether this criterion is too strict.

Medical therapy for interstitial cystitis includes a host of oral and intravesical agents as well as general pain management techniques (Table 7.6). Overall response rates vary between 50 and 90% with about a third of responders relapsing over time.

Dietary therapy may contribute to management. This involves adequate fluid intake, avoidance of soft drinks, caffeine, and citrus juices as well as a variety of other less well-substantiated recommendations.

Under the heading of functional disorders, chronic intermittent bladder spasm is an uncommon, but not rare, contributor to CPP. Ordinarily, the association with voiding makes the diagnosis as well as the suprapubic location of the pain. During pelvic examination, the bladder area may be somewhat tender, especially if the patient has just voided prior to the examination. Anticholinergic and antispasmodic agents (such as hyoscyamine sulfate [Levsin] or Donnatal) are good initial therapies, although the sedative side effects of these drugs complicate their use.

Bladder training or the bladder "drill" is often helpful in reducing the inherent irritability of the bladder in both interstitial cystitis and bladder spasm. In this exercise, the patient records the time of each urination over several days and then calculates the average interval. While maintaining a steady fluid intake throughout the

TABLE 7.6 Treatment Modalities in Interstitial Cystitis

NONSURGICAL

Pharmacologic
Antihistamines
Anti-inflammatories
Sodium pentosan polysulfate (Elmiron)
Anticholinergics

Intravesical
Dimethyl sulfoxide (DMSO)
$DMSO_2$ (investigational)
DSMO cocktails
Silver nitrate
Sodium oxychlorosene (Chlorpactin)
Cystostat (investigational)
Cromolyn (a mast cell inhibitor) (investigational)

OTHER
Electric stimulation
Biofeedback
Transcutaneous electric nerve stimulation
Epidural block
Bladder pillar block

SURGICAL

Endoscopic Procedures
Hydrodistention
Transurethral resection and fulguration
Neodymium: yttrium-aluminum garnet laser

Open Surgical Procedures
Denervation procedures
Bladder augmentation procedures
Urinary diversion

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day, the patient then voids on a schedule. She gradually increases the voiding interval over weeks or months. This accomplishes a gradual nontraumatic stretching of the bladder wall and, often, a reduction in symptoms.

Neuropathic Pain

Since the early 1990s, there has been growing recognition that pain may at times arise from nerves supplying a nociception-producing organ, sometimes even after the organ has been removed. Examples we have seen include intrinsic cervical pain to gentle touch (allodynia) after trauma such as obstetrical laceration or a loop electrosurgical excision procedure (LEEP), vulvar vestibulitis, and sensitivity of the vaginal apex (usually one fornix) after hysterectomy. In each case, creatively devising ways to deliver lidocaine 5% ointment to the sensitive area for as many hours of the day as possible has often been helpful. For the cervix, a contraceptive diaphragm can be partly filled with lidocaine and placed in the vagina overnight. For the vaginal apex, commercial lidocaine ointment or a compounded preparation can be delivered to the spot with a vaginal applicator (see the following discussion). For the vestibule, we have gotten excellent results in recent years from the twice daily application of estradiol and lidocaine compounded in hydrophilic petrolatum.

Neuropathies often present as pain that has a burning, shocklike character and may be associated with paresthesia and dysesthesia. Mononeuropathies that involve nerves originating from T10 to L4 may present as CPP. Entrapment of the ilioinguinal nerve particularly after surgery using a transverse, lower abdominal incision may also cause pelvic pain, as can pudendal neuralgia (this may also present as vulvar pain in addition to possible pelvic pain).[80-82]

Ovarian Cancer

Ovarian cancer is not as "silent" as it is often described. Many patients will report one or more nonspecific symptoms in the year prior to diagnosis including abdominal or pelvic pain.

Miscellaneous Causes

In addition to the previously mentioned disorders, a whole host of uncommon and rare conditions may produce pelvic pain. The uncommon categories would include posthysterectomy entrapment of the ovary, ovarian remnant syndrome, and intrinsic vaginal apex pain. The rarer disorders would include true peripheral neuropathies of the pelvis, traumatic neuromas, levator muscle tendinitis, and a variety of other focal pain syndromes of mixed etiology.

Following hysterectomy, reapproximation of the pelvic peritoneum may result in encasement of one or both ovaries in adhesion, sometimes at close proximity to the vaginal apex. During intercourse, percussion of the encased ovary can be quite painful. Incorporating the utero-ovarian ligament in the vaginal apex at the time of vaginal hysterectomy leads to a high frequency of post-vaginal hysterectomy deep dyspareunia. For this reason, this surgical technique is no longer recommended. Although suppression of ovarian function may reduce the discomfort, surgical removal is often necessary.

The ovarian remnant syndrome is uncommon but not as rare as previously thought. In a patient with ostensible bilateral salpingo-oophorectomy, the presence of functioning ovarian tissue is detected by withdrawing replacement hormones for 3 to 4 weeks and then determining the serum follicle-stimulating hormone (FSH) and estradiol levels. If the FSH level is well over 40 and estradiol levels are minimal, then it is highly unlikely that ovarian tissue is present. If premenopausal levels of these hormones are present, then hormonally functional ovarian tissue is present. In practice, ovarian remnants do not function like normal ovaries. Indeed, they commonly stop functioning altogether by about age 44 or 45 years. Complete suppression of the remnant with a GnRH agonist will help determine the degree to which the ovarian remnant contributes to the patient's pain. If the patient is sufficiently close to the age of 44 to 45 years, then suppression with a GnRH agonist (along with add-back estrogen as appropriate) may be continued until that age is reached. If not, surgical intervention should be contemplated. Let the GnRH agonist wear off,

allowing the remnant to grow back to a size that allows easier surgical pursuit. With the best of surgical techniques, there is a 10 to 15% chance of recurrence of the ovarian remnant after careful excision.

After hysterectomy, the vaginal apex may be intrinsically sensitive in the occasional patient. Although granulation tissue can cause this problem in the early postoperative months, localized sensitivity sometimes remains for years thereafter, well after all postoperative inflammation has disappeared. This condition is detected by gently "walking" a cotton-tipped applicator over the vaginal apex during speculum examination. Often, one part of the vaginal apex will be sensitive, whereas other parts will be quite comfortable even though the entire suture line may look perfectly normal. A local block with 1% lidocaine mixed with sodium bicarbonate (1.0 mL of 0.9% sodium bicarbonate with 9 mL of 1% lidocaine) can accomplish transient and sometimes long-term relief. Blocking the area successfully will confirm the diagnosis. Some patients can adequately cope with this disorder by using 5% lidocaine ointment delivered by a vaginal applicator. Dose titration is important in order to accomplish comfortable intercourse without producing genital anesthesia for both partners. If these conservative modalities fail, then medications commonly used for neuropathic pain (amitriptyline, nortriptyline, desipramine, Cymbalta, etc.) should be tried. Surgical revision of the vaginal apex may be helpful as a last resort, but about two-thirds of operated patients have some return of pain within 2 years of surgery. This implies that nerves severed during the revision simply grow back over time, and that treatment should be directed at their inappropriate transmission of nociceptive signals, as opposed to their simple presence.

Osteitis pubis may cause lower abdominal pain and CPP due to noninfectious inflammation of the pubic symphysis. It may result as a complication of surgery (e.g., a urogynecologic procedure), or it may be related to pregnancy/childbirth, rheumatologic disorders, or trauma. On exam, the pubic symphysis is tender to palpation.

HYSTERECTOMY FOR PAIN

Referral center clinicians who treat women with CPP often feel that hysterectomy for this condition does not work well. Examples of women who are referred for evaluation of pain continuing after surgery and very complicated women who are referred to a tertiary care center for surgery cast a negative pall over surgical intervention. However, literature describing outcomes of hysterectomy in women undergoing surgery in primary care settings is encouraging.[71,72] Taken as a whole, positive outcomes are seen in between 80 and 90% of cases in which pelvic pain was a major indication for surgery. This would suggest that, generally speaking, clinicians should employ reasonable judgment in selecting patients for surgery. Somewhat more surprising, perhaps, is that even women with chronic pain and depression before surgery substantially improved in 80% of cases when followed prospectively for 2 years after surgery. Further work needs to be done to determine what measures are needed to improve surgical results in the 20% or so of women who are more compromised at the time they have their surgery. It would seem that recognition of other components of pain would be most helpful, such as musculoskeletal pain, bladder pain, IBS, etc.

All of this being said at the same time, the practicing gynecologist should avoid the trap of performing hysterectomy because he or she has run out of other alternative treatments. Perhaps the most glaring example of this is the often quite young patient who undergoes hysterectomy and removal of both ovaries for pain attributed to minimal endometriosis after multiple laparoscopies, GnRH agonists, oral contraceptives, and other forms of ovarian suppression have not worked. In this case, if multiple therapies, each of which typically helps 80 to 90% of patients, all have NOT worked, then it seems the relevance of the diagnosis of endometriosis should be questioned rather than going on to even more aggressive surgical treatment. Almost all patients we have seen in this condition before hysterectomy have had complex pain conditions. Those seen after having hysterectomy may also be complex. When they improve after careful treatment, they then become very upset about the unnecessary hysterectomy they had at a young age.

PSYCHIATRIC CONDITIONS INVOLVED WITH CHRONIC PELVIC PAIN

Once pain has become chronic, it has a very powerful emotional meaning to the patient and to her family and friends. When concise diagnosis proves elusive, anxiety and fear of the unknown pathologic process can aggravate both the intensity of the pain and the suffering that is its consequence.

When painful events occur to a person who has substantial emotional needs that are unmet, the combination of these circumstances may support the development of one of the following styles of interaction between family members and the patient[69]:

1. The pain serves as a proxy for dysfunction in the family that is easier to tolerate than the dysfunctional relationships in the family.
2. The family acts as a re-enforcer of the pain by nurturing and caring for the patient.
3. The patient uses the pain to control the family (with this pattern unwittingly reinforced by the family).
4. The stress of the family life produces psychological effects, which predispose the patient to stress and pain.[73]

Even when these patterns are present or when obvious depression is present, this does not necessarily preclude the existence of organic pathology that requires medical and/or surgical therapy.

Much has been said and written about the association of depression with chronic pain of virtually any sort.[74,75] Depression, when associated with pain, may lower the pain threshold, thereby increasing sensitivity to pain and may be associated with irritability and social withdrawal symptomatology rather than the more dramatic symptoms of overt sadness, sleeplessness, and suicidal ideation. In most instances, the depression can be seen as coevolving with the pain disorder, not as an etiologically important precursor.

Similarly, anxiety disorders may contribute substantially to the intensity of symptoms of pelvic pain but are rarely the sole etiologic agent of the pain. Comanagement with a mental health professional is usually desirable, although the interested and experienced primary care clinician can certainly manage medication approaches for these problems.

Finally, personality disorders, somatization, and hypochondriasis can accompany any of the pelvic pain disorders. A more complete discussion of these psychological aspects of chronic pain is presented elsewhere.[83]

GENERAL PRINCIPLES OF PAIN MANAGEMENT

When confronted with CPP, the practitioner is challenged to present all possible modes of therapy in a balanced fashion. In addition, the health care provider must resist the tendency to attribute the entire symptom complex to a single disorder. It is useful to conduct a thorough educational session, which creates a list of potential contributing factors and outlines reasonable therapies. This list can be constructed only at the completion of a thorough history and physical examination and, possibly, after some preliminary diagnostic studies.

Even when surgery seems imperative, the clinician should resist the tendency to pursue maximal surgical treatment without consideration of treatment of other components. Pursuit of only one therapeutic modality reinforces the notion that CPP problems can be understood in an either/or fashion, that is, they are *either* physically caused *or* psychologically based. In the vast majority of situations, seeing the problem as one of possible centralization/neuropathic pain development will result in a more productive treatment plan and will rescue both the patient and the gynecologist from placing too much hope on the outcome of surgery.

In addition to the specific therapies described for the conditions listed previously, some general principles of medication management deserve review. An individual patient's problem list may require a pharmacologic approach to two or three conditions simultaneously. For example, the IBS may require dietary management with fiber and water additions, whereas the pain may require analgesia of either a narcotic or nonnarcotic variety, and a chronic pain syndrome may require antidepressant therapy. It is often useful to begin some or all of these medications in close proximity to each other, allowing only enough time between their initiations to evaluate the side effects accurately. Although this may result in polypharmacy initially, it is more likely to produce a greater degree of clinical improvement, thereby accomplishing a better, and perhaps quicker, return to normal function.[84]

Narcotic medications can sometimes be used on a long-term basis in the carefully selected and monitored patient. Table 7.7 describes their general dose levels and common side effects. It is useful to have the patient sign a narcotics "contract," which is basically her promise to obtain controlled substances from only one physician and one pharmacy, and to stick to a rigidly prescribed schedule.

The prescription of narcotics for chronic nonmalignant pain (CNMP) increased substantially in the early 1990s after the publication of several articles advocating the practice. From 1990 to 2004, the number of first-time abusers of prescription opioids increased from 628,000 to 2.4 million. This problem is causing an ongoing re-examination of the role of opioids in the management of CNMP.

Antidepressant medications have been a mainstay of chronic pain management of all types for many years. The best studied are the tricyclic antidepressants (amitriptyline and nortriptyline) slowly titrated up to doses of 50 to 75 mg at bedtime. If constipation is a major factor in the patient's pain, a selective serotonin reuptake inhibitor (SSRI) such as sertraline (Zoloft) or paroxetine (Paxil) rather than amitriptyline is probably a better initial treatment because SSRIs have fewer anticholinergic side effects. These latter drugs are effective for depression but lack the impact on the neuropathic component of pain that is seen with the tricyclic antidepressants.

Gabapentin and pregabalin are useful treatments for neuropathic pain, so they may be helpful in instances of pelvic myofascial pain. Gabapentin may be initiated at 100 mg at bedtime and then increased by 100 mg per week up to 300 mg three times daily. The dose may be increased further (up to 2400 mg per day maximum) depending on the patient's symptoms and side effects. Pregabalin is often initiated with 25 mg at bedtime and then increased slowly to 75 mg twice a day. Higher doses (up to 600 mg per day) may be needed. For both of these drugs, it may take 4 to 6 weeks to see an effect, and the medications must be tapered over at least 1 week prior to discontinuation.

The clinician dealing with chronic pain syndromes soon recognizes that complete success is often elusive. For the surgically oriented gynecologist who is used to a very high level of positive therapeutic outcome, this realization may prove frustrating. To survive, the successful

TABLE 7.7 Narcotics Commonly Used in Chronic Pain Management

Drug Name	Usual Dose Range	Side Effects
Hydrocodone bitartrate with acetaminophen Lortab 2.5/500, 5/500, or 7.5/500 Vicodin 5/750 Lorcet 10/650 Lorcet Plus 7.5/650 (all are scored tablets)	5–10 mg hydrocodone either q6hr or q8hr Can use additional acetaminophen between doses to potentiate effect	Lightheadedness, dizziness, sedation, nausea and vomiting, and constipation (These are common side effects of all narcotics.)
Oxycodone hydrochloride Percocet 5 mg with 325 mg acetaminophen Percodan 4.5 mg with 325 mg aspirin (also contains 0.38 mg oxycodone terephthalate)	1 tablet q6hr or q8hr Additional acetaminophen between doses may serve to potentiate effect	Common effects.
Oxycodone controlled release OxyContin	10–40 mg q12hr	Common effects.
Methadone hydrochloride Dolphine 5- or 10-mg scored tablets	2.5 mg q8hr to 10 mg q6hr Commonly 15–20 mg qd	Common effects. Lower extremity edema or joint swelling may occur and require discontinuation. Concurrent use of desipramine may increase methadone blood level. Cautious use in patients on monoamine oxidase inhibitors.
Acetaminophen with codeine Tylenol No. 3, 300 mg acetaminophen with 30 mg codeine	1–2 tablets q6–8hr	Common effects. Constipation very likely. Nausea and vomiting more common than with other narcotics. More common allergy—rash.
Morphine sulfate MS Contin or Oramorph	15–60 mg q12hr; controlled release tablets	Common effects. Higher doses increase risk of respiratory depression.
Fentanyl transdermal system Duragesic	25-μg patch, 1 q72hr Also available in 50 or 75 μg Always start with lowest dose	Common effects. Patch must be kept from heat sources, or dose may be increased. Extreme caution in patients on other central nervous system medications. Respiratory depression can result.

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clinician lowers his or her reward threshold when dealing with chronic pain patients but makes the commitment to continue the positive therapeutic relationship with the patient despite the frustrations involved. Early consultation with a specialist in chronic pain can often be fruitful and should provide the basis for an ongoing collaborative and therapeutic team approach.

THE FUTURE

Over the next several decades, the clinical science of management of chronic pain will likely undergo substantial positive change. There would seem to be three areas of research that are of great promise:

1. The role of microglia cells in pain signal modulation and as pharmacologic targets
2. Broader application of nerve blocks and medications for neuropathic pain at an earlier stage of illness
3. Development of methodologies for identifying the patient who is more at risk for developing chronic pain in the course of treating organic pathology

For the clinician struggling to help the challenging pain patient, new treatment methods emerging from this research will likely offer great hope.

CLINICAL NOTES

- CPP is pain present in the pelvis more often than not for 6 months or longer.
- Centralization of pain occurs when changes occur in the spinal cord that result in ongoing signals being sent to the brain despite the dramatic decrease or even absence of peripheral nociception.
- Spinal cord "wind-up" occurs when repeated, low-level nociceptive stimuli from the periphery elicit progressively more dramatic responses from second-order neurons at the spinal cord level, even though the intensity of the stimuli may remain constant or even be diminished.

(continues)

- When pain is prolonged and chronic, the anatomic site of the pain may become less distinct, and symptoms originating in surrounding organ systems may join the original complaint.
- Studies suggest an association between a history of abuse and CPP. Care must be taken not to automatically ascribe responsibility to this history for pain that is present.
- Examination of the patient with CPP should include a thorough abdominal examination.
- The sequence of the pelvic examination is determined by the nature, suggested source, and type of pain.
- Trigger points may be treated by injection of local anesthetics; this may also facilitate the pelvic examination.
- Possible pelvic sources for CPP include endometriosis, adhesions, adenomyosis, pelvic congestion, and neuropathic pain.
- Physical examination may not detect any abnormalities early in the disease of endometriosis, although detection of uterosacral nodularity may be enhanced by conduction of the pelvic exam during menstruation.
- Among women undergoing laparoscopy for chronic pelvic pain, adhesions are found between 45 and 90% of the time. Studies on the impact of adhesiolysis suggest laparotomy to be superior to laparoscopy only in cases of dense bowel adhesions.
- The diagnosis of adenomyosis requires histologic examination of the uterine wall. A woman with severe disease may demonstrate substantial cyclic changes in the size, consistency, and tenderness of the uterine fundus.
- The prevalence of pelvic congestion is uncertain and concrete physical findings are limited. Bimanual exam may reveal a "doughy" consistency to the parametrial areas.
- IBS may cause symptoms attributed to a gynecologic origin.
- There appears to be a fairly strong association of IBS with dysmenorrhea.
- The medical management of choice for IBS is determined by the predominant symptoms.
- Levator ani muscle spasm is a frequently overlooked finding in the patient with pelvic pain. If present, it may be helpful to teach pelvic floor relaxation exercises.
- Piriformis muscle spasm causes pain upon first arising and starting to walk, climbing stairs, and/or while driving. The pain is not related to time of day or phase of cycle. It may develop as a result of athletic injury or be associated with other inflammatory conditions.
- Musculoskeletal dysfunctions may develop as a response to initial gynecologic problems.
- Urinary tract disorders may also cause pelvic pain; examples would include pelvic relaxation, urethral diverticulum, chronic UTIs, and interstitial cystitis.
- Posthysterectomy pain may occur if the ovaries become encased in adhesions; dyspareunia may be present if the ovaries and/or ovarian adhesions are close to the vaginal apex.
- Other sources of posthysterectomy pain include ovarian remnant syndrome or hypersensitivity of the vaginal apex.
- Depression may be associated with chronic pelvic pain. Similarly, anxiety disorders, personality disorders, somatization, or hypochondriasis may also accompany a pelvic pain disorder.
- Treatment of a patient's pain may require a pharmacologic approach to two or three conditions simultaneously.
- Antidepressants, such as amitriptyline, have been a mainstay of chronic pain management of all types for many years. If the patient suffers constipation, an SSRI may be better initial therapy.

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CHAPTER 8

Premenstrual Syndromes

Meir Steiner and Tina Li

Epidemiologic surveys have estimated that as many as 75% of women of reproductive age experience some symptoms attributable to the premenstrual phase of the menstrual cycle.[1] More than 100 physical and psychological symptoms have been reported[2]; however, most women are able to manage these symptoms through lifestyle changes and conservative therapies. This phenomenon is often classified by the generic term *premenstrual syndrome* (PMS) and most often refers to any combination of symptoms that appears during the week prior to menstruation and that resolves within a week of onset of menses.[3] Conversely, 3 to 8% of women of reproductive age report premenstrual symptoms of irritability, tension, dysphoria, and lability of mood, which seriously interfere with their lifestyle and relationships.[4–11] So disruptive is the latter that a series of research diagnostic criteria for what is now labeled premenstrual dysphoric disorder (PMDD) have been developed and published in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) (Table 8.1).[12] Women who are found to meet the diagnostic criteria of PMDD do not usually respond to conservative and conventional interventions, and they often seek the expertise of a health professional.[13]

ETIOLOGY

The etiology of PMS, and specifically of PMDD, is still largely unknown. Attempts have been made to explain the phenomena in terms of biology, psychology, or psychosocial factors, but most of these explanations have failed to be confirmed by laboratory and treatment-based studies.

As is true for all female-specific mood disorders, the role of female sex hormones in PMDD has been considered of central importance. To date, however, studies attempting to attribute the disorder to an excess of estrogen, a deficit of progesterone, a withdrawal of estrogen, or changes in estrogen-to-progesterone ratio have been unable to find specific differences between women with PMDD and those without the disorder.[14] Treatment studies have suggested that progesterone and progestogens may actually provoke rather than ameliorate the cyclical symptom changes of PMDD.[15] The hypothesis that ovarian cyclicity is important in the etiology of PMDD is nevertheless supported by research. Efforts to suppress ovulation with estradiol patches and cyclical oral norethisterone, use of gonadotrophin-releasing hormone (GnRH) agonists, or bilateral oophorectomy resulted in the disappearance of premenstrual mood disturbances and physical symptoms.[16–18]

The current consensus seems to be that normal ovarian function (rather than hormone imbalance) is the cyclical trigger for PMDD-related biochemical events within the central nervous system and other target tissues. A psychoneuroendocrine mechanism triggered by the normal endocrine events of the ovarian cycle seems the most plausible explanation.[19] This viewpoint is attractive in that it encourages investigation of the neuroendocrine-modulated central neurotransmitters and the role of hypothalamic-pituitary-gonadal (HPG) axis in PMDD. Data regarding the hypothalamic-pituitary-adrenal (HPA) axis function in women with PMS are conflicting. Overall, no differences between PMS patients and controls have been observed, but more recently, there is some indication that despite the ubiquity of affective symptoms in PMS, HPA axis function in PMS is distinctly different from that seen in major depression. Women with PMS fail to show the normal increase in HPA axis response to exercise and also seem to have a blunted adrenal sensitivity.[20] They also appear to have an abnormal response to normal levels of progesterone,[21] including physical evidence for an abnormal brain response to progesterone.[22]

Of all the neurotransmitters studied to date, increasing evidence suggests that serotonin may be important in the pathogenesis of PMDD.[23–27] PMDD also shares many of the features of other mood and anxiety disorders linked to serotonergic dysfunction.[28–30] In addition, reduction in brain serotonin neurotransmission is believed to lead to poor impulse control, depressed mood, irritability, and increased carbohydrate craving—all mood and behavioral symptoms associated with PMDD.[31]

Reciprocity between fluctuations in ovarian steroids and serotonergic function has been established in animals showing that estrogen and progesterone influence central serotonergic neuronal activity.[32] In the hypothalamus, estrogen induces a diurnal fluctuation in

TABLE 8.1 Summary of Premenstrual Dysphoric Disorder *DSM-5* Criteria

A. In most menstrual cycles during the past year, five (or more) of the following symptoms occurred during the final week before the onset of menses, started to improve within a few days after the onset of menses, and were minimal or absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
   1. marked affective lability (e.g., mood swings; feeling suddenly sad or tearful or increased sensitivity to rejection)
   2. marked irritability or anger or increased interpersonal conflicts
   3. markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
   4. marked anxiety, tension, feelings of being "keyed up" or "on edge"
   5. decreased interest in usual activities (e.g., work, school, friends, hobbies)
   6. subjective sense of difficulty in concentration
   7. lethargy, easy fatigability, or marked lack of energy
   8. marked change in appetite, overeating, or specific food cravings
   9. hypersomnia or insomnia
   10. a subjective sense of being overwhelmed or out of control
   11. other physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," weight gain

B. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work, school, or home).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may co-occur with any of these disorders).

D. Criteria A, B, and C should be confirmed by prospective daily ratings during at least two symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

serotonin,[33] whereas progesterone increases the turnover rate of serotonin.[34]

More recently, several studies concluded that serotonin function may also be altered in women with PMDD. Some studies used models of neuronal function (e.g., whole blood serotonin levels, platelet uptake of serotonin, platelet tritiated imipramine [Tofranil] binding) and found altered serotonin function during all phases of the menstrual cycle.[23,35–38] Other studies that used challenge tests (with L-tryptophan, fenfluramine [Pondimin], and buspirone [BuSpar]) suggested abnormal serotonin function in symptomatic women but differed in their findings as to whether the response to serotonin is blunted or heightened.[25,39–42] These studies imply, at least in part, a possible change in 5-hydroxytryptamine (serotonin) ($5HT_{1A}$) receptor sensitivity in women with PMDD.

The current consensus is that women with PMDD may be behaviorally or biochemically subsensitive or supersensitive to biological challenges of the serotonergic system.[43,44] It is not yet clear whether these women present with a trait or state marker of PMDD.

RISK FACTORS

Epidemiologic surveys from around the world continue to demonstrate convincingly that, for adult women, the lifetime prevalence of mood disorders is substantially higher than it is among men. Most studies confirm that the ratio of affected women to men is approximately 2:1, and this ratio is maintained across ethnic groups.[45] The higher incidence of depression among women is primarily seen beginning at puberty and is less marked in the years after menopause.[46] The relationship between PMDD and other psychiatric disorders is complicated by the observation that a high proportion of women presenting with PMDD have a history of previous episodes of mood disorders and that women with an ongoing mood disorder report premenstrual magnification of symptoms as well as an emergence of new symptoms.[29,30,47–53] Likewise, several family studies have identified a concordance in rates of premenstrual tension between first-degree female family members.[54–56] Women with PMS/PMDD also report more stressful life events,[57] and more women with PMDD have histories of abuse (either sexual or physical) when compared with controls.[58,59]

PRESENTATION AND DIAGNOSIS

To aid in the study of menstrual cycle disorders, each menstrual cycle is characterized as containing two prominent phases: the follicular phase occurs after the onset of menses, and the luteal phase refers to the premenstrual interval. The temporal relationship between fluctuations in psychopathology and different phases of the menstrual cycle are well documented. It is therefore essential to ascertain whether the presenting premenstrual symptomatology is unique to the luteal phase or whether it is a worsening of an ongoing, persistent physical or psychiatric disorder.

Unfortunately, investigators have yet to reach consensus on how to best define the follicular and luteal phases of the menstrual cycle. Some investigators use set days, and others use cycle-adjusted days; other combinations also exist (Fig. 8.1). Although researchers are still defining the temporal boundaries of the follicular and luteal phases,[60] a definition of the follicular phase as days 7 through 11 after onset of bleeding and the luteal phase as 6 days before bleeding through 2 days before bleeding seems most appropriate in clinical settings.

Another challenge in the delineation of premenstrual disorders is that most women report varying combinations of the most troubling symptoms. Some investigators attempted to divide the most prominent symptoms into physical and psychological domains; however, a complete separation is not possible. Measurement tools developed for depression and other mood disorders have not performed well in the diagnosis of PMS.[61] A review by Budeiri et al.[2] identified at least 65 instruments

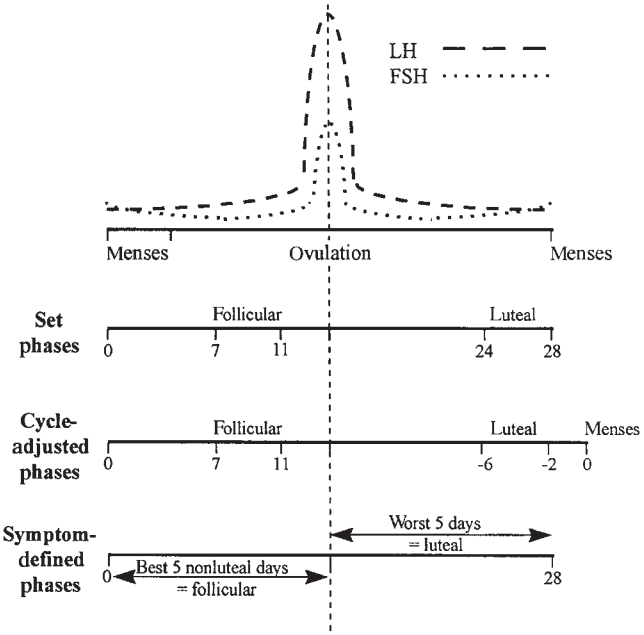

FIGURE 8.1 The follicular and luteal phases can be defined in various ways for research purposes. The cycle-adjusted phases illustrated in the middle graph seem most appropriate to clinical settings. LH, luteinizing hormone; FSH, follicle-stimulating hormone.

developed specifically to measure various combinations of premenstrual symptoms. Generally, if an instrument has been tested for reliability and validity in this population, it is appropriate for both facilitating diagnosis and assessing treatment outcomes. There has yet to be consensus as to which instruments are most appropriate for diagnosis and measurement of treatment efficacy,[2,62] so most investigators use at least two or three of these instruments in their clinical trials.

Women presenting with premenstrual complaints should be instructed to chart their symptoms daily over the course of several menstrual cycles to measure symptom change within each cycle. The current emphasis is on prospective self-report instruments, which are easy to administer and score without jeopardizing validity. The Daily Record of Severity of Problems (DRSP) assesses 20 symptoms associated with PMDD and specifically measures functional impairment in work and social realms.[63] The Premenstrual Record of Impact and Severity of Menstruation (PRISM)[64] and the Calendar of Premenstrual Experiences (COPE)[65] are detailed one-page calendars that have also been validated and used in clinical trials. Figure 8.2 is a copy of the PRISM calendar, and Table 8.2 provides the instructions for completing it. These calendars allow respondents to rate a variety of physical and psychological symptoms, indicate negative and positive life events, record concurrent medications, and track menstrual bleeding and cycle length. Additionally, a premenstrual symptoms screening tool (PSST) has been developed that scores for both PMS and PMDD (Fig. 8.3).[11]

The lack of objective diagnostic tests for PMS or PMDD mandates taking a complete history of symptoms when one of these diagnoses is suspected. In addition to a history of the premenstrual symptoms, this interview should also include a complete review of physical systems (with particular attention to gynecologic and endocrine symptoms) and medical disorders, as well as a psychiatric history and a detailed review of family history looking for mental illness. Because the symptoms of anemia and thyroid disease often mirror those of PMS or PMDD, the patient should undergo laboratory studies if there is any hint of an underlying medical cause for the symptoms. In addition, women who are suspected to meet criteria for PMDD should be assessed by their physicians at least once during each cycle phase to ensure the patient subjectively endorses phase-appropriate mood symptoms that support their daily charting (minimal or no symptoms during follicular phase, lifestyle-impairing symptoms during the luteal phase).

The essential features of the *DSM-5* PMDD criteria are the cyclicity of symptoms and the emphasis on core mood symptoms (criterion A), the requirement that the symptoms must interfere markedly with lifestyle

TABLE 8.2 Instructions for Completing the Premenstrual Record of Impact and Severity of Menstruation Calendar

Prepare the calendar on the first day of menstruation. Considering the first day of bleeding as day 1 of your menstrual cycle, enter the corresponding calendar date for each day in the space provided. Each evening, at about the same time, complete the calendar column for that day as described here:

- Bleeding: Indicate if you have had bleeding by shading/filling in the box earlier that day's date; for spotting, use an "X."
- Symptoms: If you do not experience any symptoms, leave the corresponding box blank. If present, indicate the severity by entering a number from 1 (mild) to 7 (severe).
- Lifestyle impact: If the listed phrase applies to you that day, enter an "X."
- Life events: If you experienced one of these events that day, enter an "X."
  Experiences: For positive (happy) or negative (sad/disappointing) experiences unrelated to your symptoms, specify the nature of the events on the back of the form.
  Social activities: This implies such events as a special dinner, show, or party, etc., involving family or friends.
  Vigorous exercise: This implies participation in a sporting event or exercise program lasting more than 30 minutes.
- Medication: In the bottom five rows, list medication used, if any, and indicate days when medication was taken by entering an "X."

From Reid RL. Premenstrual syndrome. *Curr Probl Obstet Gynecol Fertil.* 1985;8:1–57, with permission.

Baseline weight on Day 1 _____ lbs. or kg.
(circle one)

Bleeding																																	
Day of Menstrual Cycle Month: Date:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
SYMPTOMS																																			
Irritable																																			
Fatigue																																			
Inward anger																																			
Labile mood (crying)																																			
Depressed																																			
Restless																																			
Anxious																																			
Insomnia																																			
Lack of control																																			
Edema or rings tight																																			
Breast tenderness																																			
Abdominal bloating																																			
Bowels: const. (c) loose (l)																																			
Appetite: up ^ down v																																			
Sex drive: up ^ down v																																			
Chills (C)/sweats (S)																																			
Headaches																																			
Crave: sweets, salt																																			
Feel unattractive																																			
Guilty																																			
Unreasonable behavior																																			
Low self-image																																			
Nausea																																			
Menstrual cramps																																			
LIFESTYLE IMPACT																																			
Aggressive towards others: Physically																																			
Aggressive towards others: Verbally																																			
Wish to be alone																																			
Neglect housework																																			
Time off work																																			
Disorganized, distractible																																			
Accident prone/clumsy																																			
Uneasy about driving																																			
Suicidal thoughts																																			
Stayed at home																																			
Increased use of alcohol																																			
LIFE EVENTS																																			
Negative experience																																			
Positive experience																																			
Social activities																																			
Vigorous exercise																																			
MEDICATIONS																																			

FIGURE 8.2 The Premenstrual Record of Impact and Severity of Menstruation. Instructions for completing this calendar are provided in Table 8.2. (Reprinted from Reid RL. Premenstrual syndrome. *Curr Probl Obstet Gynecol Fertil.* 1985;8:1–57, with permission.)

(criterion B), and most important, the requirement that the disorder must be confirmed prospectively by daily ratings for at least two menstrual cycles (criterion D). Prospective daily rating of symptoms is now the only acceptable means of confirming a provisional *DSM-5* diagnosis of PMDD.

The PRISM, COPE, DSR, and DRSP calendars contain the core symptoms and most of the additional symptoms considered for the *DSM-5* diagnosis of PMDD. In using one of the daily calendars, the clinician must identify *a priori* the patient's chief complaints and the symptoms to be followed throughout treatment. Daily symptoms are rated by the patient using scales that range from none (for a score of 0) to severe (for a score of 7 on the PRISM, 3 on the COPE). Scores for the symptoms of interest are added for the 5 follicular days and the 5 luteal days, and these total phase scores are then compared.

Investigators have typically followed a diagnostic severity criterion that is applied in addition to the criteria listed for PMDD in the *DSM-5*. Conventionally, an increase in symptom scores (worsening) of at least 30% from follicular to luteal phase scores within a single cycle is required to meet PMDD criteria.[66] For inclusion

The premenstrual symptoms screening tool (PSST)

(please mark an "**X**" in the appropriate box)

Do you experience some or any of the following premenstrual symptoms which *start before* your period and *stop* within a few days of bleeding?

Symptom	Not at all	Mild	Moderate	Severe
1. Anger/irritability				
2. Anxiety/tension				
3. Tearful/Increased sensitivity to rejection				
4. Depressed mood/hopelessness				
5. Decreased interest in work activities				
6. Decreased interest in home activities				
7. Decreased interest in social activities				
8. Difficulty concentrating				
9. Fatigue/lack of energy				
10. Overeating/food cravings				
11. Insomnia				
12. Hypersomnia (needing more sleep)				
13. Feeling overwhelmed or out of control				
14. Physical symptoms: breast tenderness, headaches, joint/muscle pain, bloating, weight gain				

Have your symptoms, as listed above, interfered with:

	Not at all	Mild	Moderate	Severe
A. Your work efficiency or productivity				
B. Your relationships with coworkers				
C. Your relationships with your family				
D. Your social life activities				
E. Your home responsibilities				

Scoring

The following criteria must be present for a diagnosis of **PMDD**

1) at least one of #1, #2, #3, #4 is **severe**
2) in addition at least four of #1 – #14 are **moderate to severe**
3) at least one of A, B, C, D, E is **severe**

The following criteria must be present for a diagnosis of **moderate to severe PMS**

1) at least one of #1, #2, #3, #4 is **moderate to severe**
2) in addition at least four of #1 – #14 are **moderate to severe**
3) at least one of A, B, C, D, E is **moderate to severe**

FIGURE 8.3 The Premenstrual Symptoms Screening Tool © McMaster University. (Reprinted from Steiner M, Macdougall M, Brown E. The premenstrual symptoms screening tool (PSST) for clinicians. *Archives of Women's Mental Health*. 2003;6:203–209, with permission.)

of subjects in clinical trials, within-cycle worsening of at least 50% has been suggested.[67] The within-cycle percent change is calculated by subtracting the follicular score from the luteal score, dividing by the luteal score, and multiplying by 100:

$$[(\text{luteal score} - \text{follicular score}) \div (\text{luteal score})] \times 100\%$$

Thus, a patient presenting with a mean follicular score of 20 and a luteal score of 50 would demonstrate a within-cycle symptom increase of 60%. A change of this proportion demonstrates the cyclicity of symptomatology and is typical of women who meet criteria for PMDD.[68]

On completion of the two-cycle prospective diagnostic assessment phase, women may qualify for one of the following diagnostic categories. Applying these criteria to women who seek help for premenstrual complaints will facilitate the clinician in planning management interventions.

Premenstrual Dysphoric Disorder

Women who receive this diagnosis meet criteria for PMDD only. They have *no other concurrent* psychiatric disorder or unstable medical condition but may have a history of a past psychiatric disorder. They have charted symptoms daily for two cycles, and their chief complaints include one of the four core symptoms and at least 5 of the 11 total symptoms (see Table 8.1). Their symptoms have occurred with most menstrual cycles during the past year and have interfered with social or occupational roles. Their symptoms demonstrate clear worsening premenstrually and remit within a few days after the onset of the follicular phase. In addition, worsening between the follicular and luteal phases must be at least 30%.[69]

Premenstrual Syndrome

Women who receive this diagnosis do not meet all *DSM-5* criteria for PMDD but do demonstrate symptom exacerbation premenstrually. Symptoms may include mild psychological discomfort and feelings of bloating and weight gain, breast tenderness, swelling of hands and feet, various aches and pains, poor concentration, sleep disturbance, and change in appetite. Only one of these symptoms is required for this diagnosis, although the symptoms must be restricted to the luteal phase of the menstrual cycle, reach a peak shortly before menstruation, and cease with the menstrual flow or soon after.[3]

Premenstrual Magnification/Exacerbation

Women who receive this diagnosis may meet criteria for PMS or PMDD but are in the process of being assessed for, or have already been diagnosed with, a current major psychiatric disorder or an unstable medical condition.[53,68] Medical disorders that are commonly exacerbated during the luteal phase include migraine headaches, allergies, asthma, seizures, and genital herpes.[70] Psychiatric conditions that can be magnified include depression, anxiety, panic, bulimia, substance abuse, mania, and psychosis.[71]

Other Psychiatric Diagnosis Only

These women do not demonstrate premenstrual symptoms that meet criteria for PMDD but do meet *DSM-5* criteria for another psychiatric disorder. Women meeting criteria for recurrent brief depression or cyclothymic disorder may fall into this category, where the cyclical nature of their symptoms does not necessarily match the phases of their menstrual cycle.

No Diagnosis

In these women, the diagnosis of PMS or PMDD cannot be made and medical, gynecologic, and psychiatric screening is negative. These women experience disruptive symptoms that tend to occur throughout the cycle. It is often difficult to delineate the exact problem. Careful examination of the entire diary, especially the follicular phase, and discussion with the patient may show low-grade psychiatric or medical problems. These include situational, vocational, or marital stress, mild dysthymia, generalized anxiety disorder, personality disorders, irritable bowel syndrome, chronic fatigue syndrome, headache, fibromyalgia, or other pain syndromes, and sleep disorders.

TREATMENT

Women who present with premenstrual magnification of a major psychiatric disorder, personality disorder, or general medical disorder should be treated for the primary disorder at the discretion of the supervising clinician. Referral to an appropriate specialist is often indicated for newly diagnosed disorders.

A wide range of therapeutic interventions have been tested in the treatment of premenstrual symptoms, from lifestyle changes to advanced hormonal treatment.

Conservative Therapies

It is prudent to start all women with premenstrual symptoms on a program of lifestyle changes (Table 8.3). For women who do not meet criteria for PMS, PMDD, or other physical or psychological disorders, management without pharmacologic interventions should be encouraged. Unfortunately, there have been few randomized controlled trials to determine the efficacy of these more conservative interventions. There is some evidence, however, to support that these patients may best

TABLE 8.3 Conservative Treatment Modalities for Premenstrual Symptoms

Diet

Reduce or eliminate (especially in the luteal phase) salt, chocolate, caffeine, and alcohol
Small frequent complex carbohydrate meals
Vitamins and minerals in moderation

Moderate, Regular Aerobic Exercise

Stress Reduction

Stress management course and/or counseling if necessary
Relaxation course or audio tape
Assertiveness course and/or marital counseling if necessary

Self-Help Books, Groups if Available

TABLE 8.4 Evidence-Based Low-Risk Treatment Options for Premenstrual Symptoms

	Dosage
Vitamin B_6	50–150 mg daily
Calcium	1200–1600 mg daily
Magnesium	360 mg daily for the 14 days prior to menses
Optivite	Up to 6 tablets daily
Vitamin E	400 IU daily
Spironolactone	100 mg daily from day 12 until the first day of the next menstrual cycle for bloating
Bromocriptine	1.25–7.5 mg daily during luteal phase for premenstrual mastodynia

respond to individual or group psychotherapy in combination with lifestyle changes.[72,73] Recommended dietary changes (especially during the luteal phase) should include the reduction or cessation of tobacco, chocolate, caffeine, and alcohol consumption. Some women report improvement with small, frequent, complex carbohydrate meals with vitamin and mineral supplements. Patients should be encouraged to decrease sodium in their diets when edema or fluid retention occurs and, if possible, to reduce weight to within 20% of ideal weight. Regular exercise is important and particularly effective when combined with the regular practice of stress management techniques. Patients should also be taught to review their own monthly diaries and identify triggers for symptom exacerbation.

Evidence-Based Low-Risk Therapies

Women who meet criteria for PMS should be encouraged to practice the lifestyle changes described previously, but they may also respond to some of the tested low-risk therapies (Table 8.4).

Vitamin B_6 has demonstrated mild to moderate efficacy in relieving PMS symptoms in clinical trials, using a wide range of dosing strategies from 50 to 500 mg daily.[74] Because of reports of sensory neuropathy, dosing in clinical practice should not exceed 150 mg daily, given during the last 2 weeks of each cycle.

Calcium (1200 to 1600 mg daily) demonstrated significant improvement in overall symptoms scores from baseline compared with placebo.[75,76] No untoward side effects were reported with this dose.

Optivite (Optimox Corp., Torrance, CA) is a vitamin/mineral supplement. In one clinical trial, subjects were randomized to 6 or 12 tablets daily of the supplement or placebo for three menstrual cycles and demonstrated significant treatment effects in physical symptoms and depression.[77] No unusual side effects were reported. Up to six Optivite tablets daily during the luteal phase of the menstrual cycle may relieve symptoms.

Chasteberry (*Vitex agnus castus*) extract was shown to be superior to placebo in reducing the mood and physical symptoms of PMS in several prospective randomized controlled trials.[78–80] Another study found that chasteberry may be more beneficial for physical rather than psychological symptoms.[81] Although mild adverse effects have been reported, chasteberry appears to be a safe and well-tolerated treatment.

Evening primrose oil (gamma-linolenic acid) has not demonstrated efficacy superior to placebo in several randomized controlled trials and should not be recommended as treatment for PMS or PMDD.[82]

Naproxen sodium (Anaprox, Aleve) improved pain and premenstrual behavior changes in one randomized trial when taken 7 days premenstrually[83] and menstrual migraine specifically in another randomized trial when it was taken daily.[84]

Mefenamic acid (Ponstel) was superior to placebo for improving physical and mood symptoms in one randomized controlled trial[85]; however, the use of this medication should be limited (7 to 10 days) because of gastric side effects.

Spironolactone (100 mg daily) from day 12 of the menstrual cycle until the first day of the next menstrual cycle significantly reduced bloating compared with placebo in one randomized controlled trial.[86] The potential for diuretic abuse and hyperkalemia (and thus contraindication of potassium supplements) necessitates the use of this drug for severe symptoms only.

Bromocriptine (at least 5 mg daily) has demonstrated significant improvement in premenstrual mastodynia[87] but has not demonstrated efficacy with the mood symptoms associated with the premenstruum. Randomized controlled trial evidence suggests that a dosing range of 1.25 to 7.5 mg daily during the luteal phase of the menstrual cycle is appropriate for clinical use.

Women who continue to experience severe premenstrual symptoms after the commencement of lifestyle changes and the previous conservative therapies may be considered for the pharmacologic treatment regimens indicated for PMDD.

Pharmacotherapies

Therapeutic interventions for women who meet criteria for PMDD but fail conservative therapies are available. These range from treatment of the most troublesome symptoms with psychotropic medications (Table 8.5) to hormonal therapy to eliminate ovulation.

It is important to note that only studies that used prospective diagnostic criteria that could meet *DSM* PMDD classification have been cited.

Psychotropic Medications

Serotonin reuptake inhibitors have proven to be very successful in the treatment of PMDD symptoms. Of the selective serotonin reuptake inhibitors (SSRIs), fluoxetine (Prozac) 20 mg daily has been proven superior to placebo in several randomized trials.[67,88–93] One of these trials used a higher dose, 60 mg daily, but the improvement demonstrated by this group did not differ from the 20-mg group, and the side effect profile was significantly higher at the 60-mg dose.[67] Sertraline (Zoloft) 50 to 150 mg daily,[94] paroxetine (Paxil) 10 to 30 mg daily,[95] citalopram (Celexa) 10 to 30 mg daily,[96] and the selective serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor) 50 to 150 mg daily[97,98] have also demonstrated efficacy in randomized controlled trials in the treatment of PMDD. More recent studies have demonstrated the efficacy of intermittent serotonin reuptake inhibitor dosing during the last 2 weeks of the menstrual cycle.[99–101] The tricyclic antidepressant (but primarily serotonin reuptake inhibitor) clomipramine (Anafranil) has also been proven superior to placebo in two randomized controlled trials. One study used 25 to 75 mg daily[102] and the other the same dose range for only the luteal phase of each menstrual cycle.[103] Thus, the serotonin reuptake inhibitors to date have demonstrated their effectiveness in significantly improving the psychological and physical symptoms of PMDD compared with placebo, with only mild, mostly tolerable side effects. The side effect profile is similar among agents in the class; the most troublesome include headache, nausea/gastrointestinal upset, sleep disturbance/insomnia, tremulousness, sweating, dry mouth, and anorgasmia. These side effects can usually be managed through dosing changes, the use of intermittent versus daily dosing schedules, or by switching to other serotonin reuptake inhibitor compounds.

TABLE 8.5 Psychotropic Medications for Premenstrual Dysphoric Disorder and Premenstrual Syndrome Refractory to Conservative Treatment

	Dosage
First-Line Treatment: Antidepressants	
Luteal phase only or continuous	
Citalopram	10–30 mg daily
Clomipramine	25–75 mg nightly
Fluoxetine	20 mg daily
Paroxetine	10–30 mg daily
Sertraline	50–150 mg daily
Venlafaxine	25–75 mg twice a day[a]
Second-Line Treatment: Anxiolytics	
Luteal phase only	
Alprazolam	0.25–2 mg three to four times daily (max 5 mg daily)
Buspirone	10–15 mg twice a day

[a]An extended-release preparation is also available—venlafaxine-XR 75–150 mg daily.

Anxiolytics have been tested for the treatment of PMDD because of its mood disorder component. Alprazolam (Xanax) has successfully alleviated the symptoms of PMDD in several,[104–107] but not all,[108] randomized controlled trials. The risk of dependence and concerns regarding withdrawal prompted investigators to test the efficacy of alprazolam versus placebo when administered in the luteal phase only. Patient-modified dosing was allowed, and efficacious dosing ranged from 0.25 to 5 mg daily from 6 to 14 days before menstruation. One study also allowed women who demonstrated mild follicular symptoms to take this medication as needed during the follicular phase of the cycle.[106] Sedation and drowsiness were the two most frequently identified side effects of this treatment. Significant improvements in mood and physical symptoms were reported for the positive studies. The 5-HT_{1A} receptor partial antagonist buspirone (BuSpar) has also demonstrated efficacy in one randomized controlled trial when administered with a mean daily dose of 25 mg for the 12 days prior to menstruation.[109]

Hormonal Therapies

GnRH agonists can reversibly suppress the menstrual cycle, and this is often referred to as medical oophorectomy or medical menopause. GnRH agonists have proven to be very successful in clinical trials.[16,17] Unfortunately, the long-term (more than 6 months cumulative) use of GnRH agonists has been inhibited by the occurrence of side effects that mimic menopause and the potential for hypoestrogenism and osteoporosis. The "add-back" of estrogen and progesterone to goserelin (Zoladex)[110] or leuprolide (Lupron)[21] has led to the reappearance of mood and anxiety symptoms. Because it has been shown that women with severe PMS and PMDD have an abnormal response to normal hormonal fluctuation,[21] it is not surprising that the addition of hormones led to the induction of mood and anxiety symptoms, in turn reducing the benefit of the hormone replacement therapy.

More recently, a trial of women receiving leuprolide with added tibolone (a compound with some estrogenic activity) versus added placebo reported equal efficacy for premenstrual symptoms and fewer hot flushes.[18]

Estradiol treatment can suppress ovulation and thus has been proven effective in reducing the symptoms of

PMDD, although adjunct progestogen therapy is necessary to prevent endometrial hyperplasia. Luteal phase–only administration of conjugated estrogen (Premarin) was ineffective in one randomized controlled trial[111]; however, transdermal estradiol (Climara, Estraderm, Vivelle) or estradiol implants combined with luteal phase norethisterone, medroxyprogesterone (Premarin), or dydrogesterone improved physical and mood symptoms in three randomized controlled trials.[112–114] Transdermal estradiol (100- to 200-mcg patches) applied twice weekly with low-dose progestogen daily from days 17 to 26 of each cycle is appropriate for clinical use.

Danazol (Danocrine), a synthetic androgen, alleviates symptoms of PMS when administered at 200 to 400 mg daily.[115] A more recent study reported that luteal phase–only danazol was not effective for general premenstrual symptoms but was highly effective for the relief of premenstrual mastalgia.[116] Although danazol has been proven to be superior to placebo in several randomized controlled trials,[115,117–119] the adverse effect profile of this treatment is considerable and may be the result of both its androgenic activity and antiestrogen properties. Tested doses include 100 to 400 mg daily, and both mood and physical symptoms improved significantly when compared with placebo. The most prominent side effect at doses over 200 mg was altered menstrual cycle length, but at higher doses, women can get acne, bloating, depression, and permanent lowering of the voice. One study of women with PMS found that intermittent danazol, 200 mg given daily from the onset of symptoms to the onset of menses, significantly improved mood symptoms and bloating compared with placebo.[120] Clinical dosing at 200 to 400 mg daily during symptoms is appropriate.

Progesterone has been shown to be no more effective than placebo in treating PMS or PMDD symptoms in the majority of trials and should not be used as a primary treatment for these disorders.[121] Despite this mounting evidence demonstrating their lack of efficacy, progestogens, including progesterone, are the most widely prescribed treatment for PMS in the United Kingdom.[122]

Oral contraceptives suppress ovulation while maintaining menstruation with periodic steroid withdrawal. They have been commonly prescribed for the treatment of PMS even though there were few studies demonstrating their efficacy until recently. An initial report on the effectiveness of a new oral contraceptive (Yasmin) containing a combination of drospirenone (with spironolactone-like activity) and estradiol has renewed the interest in this type of intervention for women with PMDD.[123] More recently, two randomized controlled trials with YAZ (Bayer HealthCare), an oral contraceptive containing ethinyl estradiol 20 μg and drospirenone 3 mg, administered as 24 days of active pills followed by a 4-day hormone-free interval (24/4) found it to be superior than placebo in reducing premenstrual mood and physical symptoms.[124,125] The reported adverse effects include nausea, intermenstrual bleeding, and breast pain. In 2006, The U.S. Food and Drug Administration (FDA) approved YAZ for the treatment of PMDD in women seeking or already taking oral contraception, and a recent Cochrane Database systematic review supports its efficacy.[126]

To date, no one pharmacologic intervention has proven to be effective for all women with PMDD. Serotonin reuptake inhibitors continue to prove efficacious in women with PMDD who have failed conservative treatment and are currently the first treatment of choice. The new drospirenone-containing oral contraceptive presents an effective treatment option of PMDD in women desiring oral contraception. Alprazolam and buspirone have demonstrated efficacy in the reduction of psychological symptoms in randomized controlled trials, but side effects and dependence concerns with the benzodiazepines limit their efficacy.

The last line of treatment for women with PMDD who do not report efficacy with the symptom-modifying drugs are the GnRH agonists. Due to the potential long-term side effects of this treatment, low-dose estrogen-progesterone add-back should be considered but is likely to affect efficacy. Estradiol and danazol may also be effective, and gynecologic interventions such as surgery may need to be considered.[127,128]

ASSESSMENT OF TREATMENT EFFICACY

Patients should be assessed every 2 weeks (i.e., during both the follicular phase and the luteal phase) within the first month of commencing any therapy, and they should be instructed to continue to chart symptoms daily for at least two to three additional cycles. Dosing strategies vary, but most recent investigations demonstrated the efficacy of most therapeutic drugs at low doses. If efficacy has not been attained after several dose increases, alternative treatment options should be considered. There is increasing evidence that treatment effect is seen relatively quickly in this population. Therefore, if there is no change in symptomatology, an alternate therapy should be considered within two to three menstrual cycles. Continued symptom charting using a daily calendar will help track efficacy, symptom response to dosing changes, symptoms on termination of therapy, and side effects. For example, women who report headaches or nausea as side effects are often surprised to see that they rated these symptoms just as severe prior to commencing therapy.

Investigators have yet to reach a consensus on how to define efficacy. Clinically, the easiest way to define efficacy is by the reduction of luteal symptoms so the luteal symptoms remit significantly or the within-cycle percent change is minimal.

What has become obvious is that the intervention alone cannot predict efficacy, and more consideration is now being given to past psychiatric history and to family psychiatric history, especially of mood disorders in women with PMDD.

CLINICAL NOTES

ETIOLOGY

- The etiology of PMS and PMDD is still largely unknown.
- The current consensus seems to be that normal ovarian function (rather than hormone imbalance) is the cyclical trigger for PMDD-related biochemical events within the central nervous system and other target tissues.
- Evidence suggests that serotonin may be the predominant neurotransmitter involved.

PREVALENCE

- Epidemiologic surveys have estimated that as many as 75% of women with regular menstrual cycles experience some symptoms of PMS. The majority of these women do not require medical or psychiatric interventions.
- PMDD, however, is much less common, affecting only 3 to 8% of women in this age group. It is much more severe, specifically exerting a much greater psychological toll.

PRESENTATION AND DIAGNOSIS

- *DSM-5* lists criteria for PMDD (Table 8.1). Women who do not meet these criteria may be categorized with PMS, premenstrual magnification (of a psychiatric or medical condition), other psychiatric diagnosis only, or no diagnosis.

TREATMENT

- Conservative treatment is used for all patients, including those with premenstrual complaints but no diagnosis.
- Low-risk/evidence-based modalities, including vitamins, minerals, and nonsteroidal anti-inflammatories, are used for women with PMS or PMDD.
- Psychotropics such as serotonin reuptake-inhibiting antidepressants or anxiolytics may be useful for women with PMDD or PMS refractory to conservative treatment.
- Hormonal therapies should be reserved for refractory PMDD patients because of the adverse effects associated with "medical menopause."
- The new drospirenone-containing oral contraceptive can be used to treat PMDD in women desiring oral contraceptive.

ASSESSMENT OF EFFICACY

- Patients should continue charting their symptoms. If on pharmacologic therapy, the physician should evaluate them during both the follicular phase and the luteal phase of at least one cycle.

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CHAPTER 9

Women and Sexuality

Marianne Brandon

Few subjects generate as much interest, concern, confusion, controversy, and emotion as sex. Human sexuality is a broad concept that incorporates interactions among a wide variety of factors, for example, anatomy, physiology, interpersonal relationships, and sociocultural factors. It is helpful to approach sexuality as a paradigm that represents the intersection of factors influencing both gender (personal, psychological, and culture constructs that reference various characteristics as "male" or "female") and sex (biology) (Fig. 9.1). Sexuality and sexual health are topics relevant to all women, from adolescence through old age. As our culture becomes increasingly sexualized via the media and the Internet, women struggle more and more with sexual concerns. A woman's relationship with her sexuality relates to her sense of self at the deepest and most profound of levels. It impacts her experience of herself as a woman and her sense of personal power in the world. It is common for women to silently struggle with questions such as "Do I take too long to orgasm?" "Why can't I have a vaginal orgasm?" "Am I sexually attractive?" or "Are my sexual fantasies normal?" Our culture promotes myths about female sexuality that encourage unhealthy expectations in women. For example, we embrace the notion that if a woman marries the "right" man, her sex life will automatically be active and satisfying. In reality, couples have to work to keep their sexual relationship gratifying over time. The belief that only young women are sexual is equally damaging. In truth, most middle-aged women know their bodies better and are more experienced at giving and receiving sexual pleasure than young women. Further, the idea that most people do not have sexual problems or concerns leaves women (and men) with sexual dysfunction feeling alone and ashamed. In actuality, research shows that 43% of women and 31% of men report a sexual dysfunction.[1]

Most women agree that a satisfying sexual relationship is a key aspect of their intimate connection with their partner(s). Research indicates that adults who are sexually gratified tend to be happier in their relationships and physically healthier than those who are not sexually satisfied.[2] Attending to your patients' sexual issues can thus have a significant positive impact on their lives physically, emotionally, and interpersonally. Unfortunately, however, addressing female sexual dysfunction is not simple. First of all, there is the issue of time. Evaluation of a sexual complaint cannot be fit in to the 7 or so minutes allotted to each patient in the busy OB/GYN practice. The economics of time and insurance reimbursements simply do not allow such an effort. Second, most clinicians do not have the background information to support active participation in the sexual interview. Sexual medicine is part of the standard medical school curriculum in too few centers around the country. And finally, there exists much controversy about the assessment and treatment of most of the diagnoses we review here. This is largely because the field of female sexual dysfunction is relatively new. Prior to a decade ago, most of the sexuality research focused exclusively on men. As our knowledge of the field grows, it is evident that men and women are very different sexual beings, and research findings cannot be easily generalized from one gender to the other. More recently, researchers have begun to focus on women subjects. However, placebo effects are significant and they complicate the interpretation of results.[3] The benefit of just opening communication channels, coupled with a patient's positive expectation of results, drives this high placebo effect.

SEXUALITY THROUGH THE LIFE CYCLE

Although we tend not to think in these terms, children are sexual beings. To their parent's dismay, toddlers can discover that masturbation feels good. Even before adolescence, children become consciously aware of their sexuality. Children growing up in Western societies are constantly bombarded with sexual images via multiple media outlets such as billboards, the Internet, and TV. Children's sexual experiences can and do impact their sexual experiences as adults. For example, instances of sexual pleasure as children can play a pivotal role in an adult's sexual fantasies. Also, how parents respond to a girl's budding sexuality in puberty will impact how she perceives her sexual self as an adult.

Adolescent girls reach puberty and sexual maturity at earlier ages than ever, with the average of menarche now at 12.5 years of age.[4] Approximately 50% of high school teens report having had sexual intercourse, and about a third report being currently sexually active.[5] Studies show that about 5% of teens identify as lesbian, gay, or bisexual, and over 10% of girls and 2 to 6% of boys report having experienced same-sex sexual activity.[6,7] Although adolescent development varies depending on the chronological age and level of maturity of the individual, by

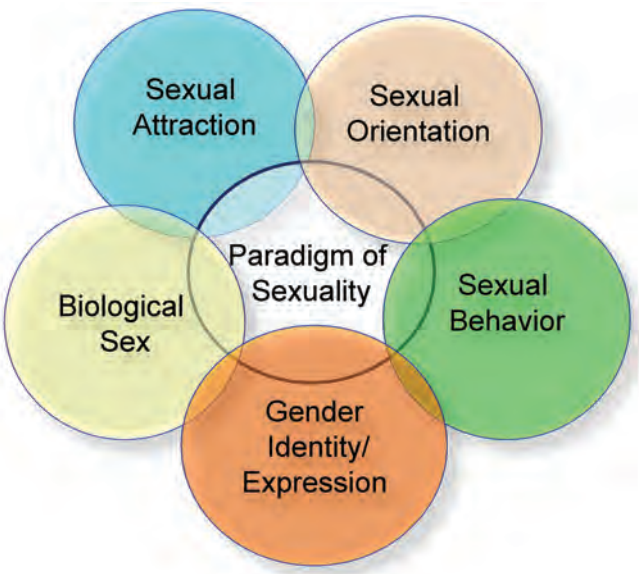

FIGURE 9.1 Paradigm of sexuality. (From Physicians for Reproductive Health. Beyond abstinence and risk: a new paradigm for adolescent sexuality. http://prh.org/teen-reproductive-health/arshep-downloads/. Accessed November 24, 2013.)

midadolescence (ages 15 to 18 years), many teens start to have romantic relationships and may engage in risk-taking behaviors such as unprotected sexual activity or substance use. Teens who engage in oral sex are likely to participate in vaginal sex soon thereafter, that is, within the next 2 years on average.[8] It is important for providers to address issues of sex education, pregnancy, contraception, sexually transmitted infections, including HIV, and teen-dating violence or date rape with all adolescents, regardless of sex or sexual orientation. Young women struggle with their own set of sexual challenges and concerns. The cultural stereotype is that women in their late teens and 20s are the sexiest and most sexual of all age groups. Interestingly, they report as many sexual dysfunctions as other age groups.[1] Thus, the most sexualized women in our culture are also very concerned about their sexuality. At the other end of the age continuum, elderly women have their own sexual struggles. In a culture that expects them to be uninterested in sex, it can be difficult for older women to seek help for their sexual concerns. In truth, women of all ages often assume they are alone with their sexual issues, leaving them feeling ashamed and embarrassed. Simply informing your patients that their concerns are common can go a long way in alleviating their distress.

DIFFERENCES BETWEEN MALE AND FEMALE SEXUALITY

Men and women are very different sexual beings. "Sexual interest, motivation, arousal, and pleasure are triggered and experienced quite differently by men and women."[9] Historically, Masters and Johnson proposed a physiologic model of normal sexual function describing a linear progression from excitement to plateau, to orgasm, and then resolution. This model may still, by and large, be applicable to men, but it is clear that the female sexual response cycle has more dimensions that must be considered in addressing sexual health and sexuality issues (Fig. 9.2). For many women, the phases of the sexual response cycle may repeat, be absent, overlap, or occur in different sequence during their sexual encounters. Unfortunately, most women compare their sexual reactions to their male partners, expecting to have similar desire patterns and responses (Table 9.1). For instance, a response to pleasurable activity may trigger desire that was not there initially. These differences may leave women feeling deficient or dysfunctional. Some of the ways men and women are different sexual beings include the following:

- In women, there is overlap among the various sexual dysfunctions, whereas men's sexual dysfunctions

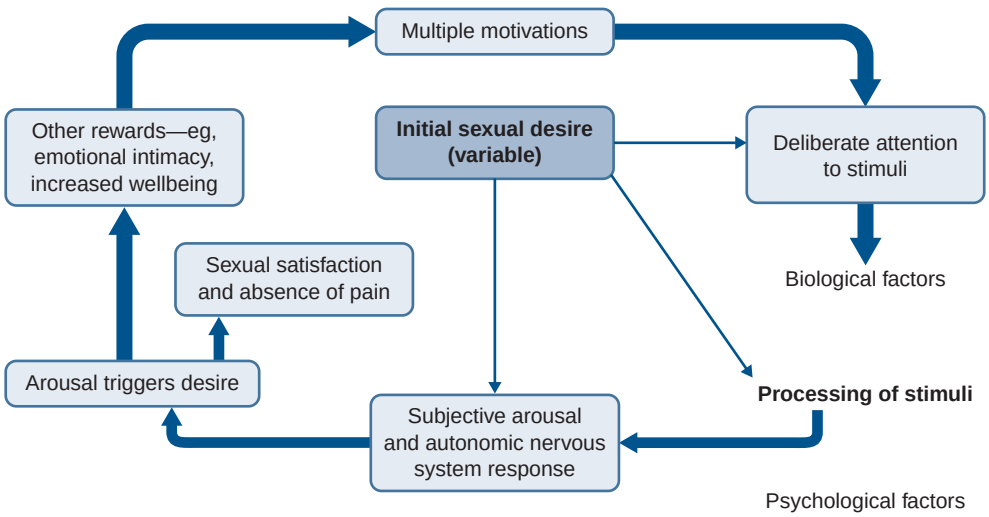

FIGURE 9.2 Circular model of human sexual response showing cycle of overlapping phases. (From Basson R, Schultz WW. Sexual sequelae of general medical disorders. *Lancet*. 2007;369:412; Adapted from Basson R. Female sexual response: the role of drugs and the management of sexual dysfunction. *Obstet Gynecol*. 2001;98[2]:350–353.)

TABLE 9.1 Sexual Response Cycle

Cycle Phase	Features	Gender Differences
Desire	Physiologic factors (neurotransmitters, androgens, and sensory system) and a wide variety of environmental stimuli (psychosocial and cultural factors) Desire causes a person to initiate or be receptive to sexual activity.	Women: touch, verbal stimuli, and relationship of greater import Men: visual stimuli of greater import
Arousal	Parasympathetic nervous system and vascular system Breathing becomes heavier, heart rate and blood pressure increase, and reflexive vasocongestion occurs.	Women: vaginal lubrication and enlargement of clitoris Men: penile erection
Plateau	Parasympathetic nervous system and vascular system Vasocongestion phase is at its peak; sexual tension increases and then levels off immediately before orgasm; there are carpopedal spasms, generalized skeletal muscular tension, hyperventilation, tachycardia, and increased blood pressure (by 20 to 30 mm Hg systolic and 10 to 20 mm Hg diastolic).	Women: maximal vaginal lubrication and genital vasocongestion Men: distension of penis to its capacity
Orgasm	Sympathetic nervous system and muscle tone For both sexes, there is heightened excitement to a peaking of subjective pleasure, followed by release of sexual tension; awareness of other sensual experiences is diminished, and the person becomes self-focused; pelvic response consists of involuntary contractions and myotonia; tension may be felt and seen in neck and face (grimaces), buttocks, thighs, and toes; there are carpopedal spasms, contractions of arms and legs, external rectal sphincter contractions, external urethral sphincter contractions, hyperventilation (up to 40 breaths per minute), tachycardia (up to 180 beats per minute), and increased blood pressure (by 30 to 80 mm Hg systolic and 20 to 40 mm Hg diastolic).	Women: contraction of uterus from fundus toward lower uterine segment, and contractions of orgasmic platform (five to 12 contractions at 0.8-second intervals) Men: with emission, semen spurts out of fully erect penis (three to seven ejaculatory spurts at 0.8-second intervals); contractions of internal organs and signal of ejaculatory inevitability (roughly 1 to 3 seconds before start of ejaculation) are followed by rhythmic contractions of penile urethra and perineal muscles (experienced as orgasm proper); after orgasm, the man is refractory to sexual stimulation for a period of time before he can be stimulated to orgasm again.
Resolution	Sympathetic nervous system Body returns to pre-excitement phase as vasocongestion is relieved and hyperventilation and tachycardia decrease.	Women: ready return to orgasm with slow loss of pelvic vasocongestion Men: in very young men, a second ejaculation may occur without loss of erection; in older men, involution of penis occurs more rapidly, often within minutes.

From Nusbaum MRH. Sexual health. Monograph no. 267, Home Study Self-Assessment Program. Leawood, KS: American Academy of Family Physicians, 2001; In: Nusbaum MRH, Hamilton C, Lenahan P. *Chronic Illness and Sexual Functioning.* 2003;67(2):347.

tend to be more distinct and specific.[10] For example, desire and arousal disorders often co-occur in women, whereas with men, premature ejaculation and low libido are more separate diagnoses.

- Women tend to experience emotional complaints about sex more than men do. Men typically seek treatment for problems with sexual performance, whereas women are more concerned about sexual feelings.[9]
- For women, lack of spontaneous sexual desire is considered within the realm of normal—particularly among older women and those in longer term relationships.[11]
- Women's response to sex is more multidimensional than men's.[12] A woman's reactions rely on much more than her body's sexual response. She places great importance on her thoughts and feelings. For women, sex is highly contextual.
- Women's experience of arousal is subjective.[13] That is, there is a poor correlation between her actual genital arousal and her subjective sense of being aroused.
- There is a fairly strong relationship between men's sexual interests and genital arousal. For women, the link between objective genital arousal and their sexual interests or even subjective arousal response is not as strong; for women, objective genital arousal seems to be provoked by nonspecific sexual features.[14]

In spite of these complexities, women's bodies are capable of more sexual pleasure than men's bodies in that many women can have multiple orgasms as well as orgasms that typically involve more muscle contractions. Because she has no refractory period, she is capable of having sex as often as she chooses. In contrast, men in general have a higher level of desire—they are more apt to masturbate, go to strip clubs, watch porn, report more sexual fantasies, desire more frequent sex with more diverse partners, engage in fetish behaviors, and show interest in more varied sexual practices.[15] These differences between male and female sexuality often leave the sexes at odds with each other, frustrated and confused.

TALKING WITH YOUR PATIENTS ABOUT SEX

Talking with patients about sexual issues can be challenging for practical as well as personal reasons. First, sexual matters require time and sensitivity to discuss. Simply finding a few minutes for sympathetic dialogue can be difficult. Plus, providers sometimes feel uncomfortable discussing personal and intimate issues with patients. However, research consistently indicates that patients frequently have sexual concerns they would like to discuss with their health care providers.[16] Many patients are too self-conscious to bring these up without an invitation. In one survey, 85% of adults wanted to discuss sexual issue with their provider, but 71% thought the provider would not want to or would not have the

time, 76% thought no treatment was available, and 68% were worried about *embarrassing their provider*.[17] As a result, patient's sexual concerns may remain unaddressed unless the physician takes the initiative to discuss them. Although all patients should be asked about their sexual health and if they have any sexual concerns or questions, there are specific gynecologic situations that clearly warrant screening for sexual dysfunction (Table 9.2).

Patients expect their physicians to be knowledgeable about female sexuality and dysfunction. Today's patients are already educated from the Internet and the regular attention paid to sexual issues in the media. The sheer prevalence of female sexual concerns leaves a clinician as an important source of information about female sexual dysfunction regardless of whether he or she desires this role.

One simple way to initiate a discussion is to acknowledge to patients that sexual concerns are very common for women of all ages. Invite patients to discuss any issues they have about their sexual functioning, such as possible sexual side effects of medication, age-related sexual changes, or to clarify information they may have learned in the media or on the Internet. This simple invitation gives patients the control to decide whether or not to pursue this dialogue. Do not be surprised if patients initially decline the discussion but then initiate the topic at a later appointment. Start the dialogue with a simple "Are you sexually active?" This is a very appropriate question to ask during the general history taking. A calm demeanor will help diffuse the anxiety this question may provoke. If the patient says yes, ask her, "Do you have any sexual health questions or concerns that you would like to discuss?" If she says no, respond with, "Does that bother you or your partner?" Be prepared for the possibility that a long conversation will ensue. This may in fact be the first time she has verbalized her very personal and intimate concerns. Be respectful of confidentiality and initiate the discussion privately when her partner is not in the room. Take care to individualize the conversation according to the patient's age, sociocultural background, and sexual orientation. It is important to focus on the positive aspects of sexuality for women during the conversation, that is, the beneficial effects of sexual satisfaction on overall physical health and relationship well-being.

Many patients will likely hope for a quick fix, such as a pill or hormone injection. Unfortunately, sexual problems are rarely so clear-cut that a single medical intervention

TABLE 9.2 Screening for Sexual Problems

Situation in Which Screening Question Is Necessary	Suggested Screening Question
Before surgery or instituting medication or hormone therapy	*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?*
Routine antenatal visit	*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.*
Complicated antenatal visit	*These complications may well have already caused you to stop being **sexual**. Specifically, you should not (have intercourse/have orgasms).*
After one or more miscarriages	*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.*
Infertility	*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?*
Postpartum	*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?*
Perimenopause or postmenopause	*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?*
Woman who is depressed	*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?*
Chronic illness	*Arthritis/multiple sclerosis can interfere with a woman's sex life. Are you having any problems?*
Potential damaging surgery	*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?*
Bilateral oophorectomy	*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?*

From Berek JS, ed. *Berek and Novak's Gynecology*. 14th ed. Baltimore: Lippincott Williams & Wilkins; 2006.

solves the problem. When there are no easy answers, this can result in a physician feeling ineffectual and disempowered. The best approach in these moments is to remain compassionate, sympathize with the patient's discomfort, and offer more complex but potentially more effective alternatives. Creating effective referral networks can greatly assist providers' effectiveness because many sexual issues are multidetermined and thus too complex for a single professional to treat effectively.

Cultural sensitivity is becoming an increasingly important issue for all physicians as world cultures continue to blend geographically. Cultural and religious values significantly impact people's experience and expectations of sex as pleasurable or as something to be controlled. They will also influence a patient's receptivity and interest in discussing his or her sexual concerns. During a sexual interview, directly asking patients what they learned about sex from their culture or religion is a straightforward way to identify how these issues may impact a particular patient. Being sensitive to patient's cultural background enables more effective communication about sexual issues.

For guidelines in taking a sexual history, see Table 9.3. The discussion should clearly be held with a nonjudgmental attitude. If the ensuing conversation makes the provider uncomfortable, it is best to refer the patient to a medical or psychological specialist in sexual functioning. It is important for providers to acknowledge that everyone has biases when it comes to sexual matters, and they must actively prevent their personal beliefs from influencing their responses when assisting patients with sensitive issues. There are professional societies that provide assistance and advice to providers around the complex issues of sex and sexuality, such as the International Society for the Study of Women's Sexual Health (www.ISSWSH.org).

TABLE 9.3 Components of the Sexual History for Assessment of Female Sexual Dysfunction

Area	Specific Elements
Medical history (past and current)	General health (including physical energy level and mood), drugs, pregnancies, pregnancy terminations, STDs, contraception, use of safe sex practices
Relationship with partner	Sexual orientation, emotional intimacy, trust, respect, attraction, communication, fidelity, anger, hostility, resentment
Current sexual context	Presence of sexual dysfunction in partner, activities and behaviors during the hours before attempts at sexual activity, presence of the following: • Inadequate sexual stimulation • Unsatisfactory sexual communication • Disagreement with partner about sexual practices or timing (eg, too late at night) • Lack of privacy
Effective triggers of desire and arousal	Books, videos, dates, showering together, dancing, music, type of stimulation (nonphysical, physical nongenital, or penetrative or nonpenetrative genital)
Inhibitors of arousal	Fatigue, stress, distractions such as negative past sexual experiences and fears about outcome (including loss of control, pain, unwanted pregnancy, and infertility)
Orgasms	Presence or absence, response to absence (whether the woman is distressed or not), differences in responses with partner and with self-stimulation
Outcome	Emotional and physical satisfaction or dissatisfaction
Location of pain in dyspareunia	Superficial (introital) or deep in pelvis
Timing of pain in dyspareunia	During partial or full entry, deep thrusting, penile movement, or the man's ejaculation; immediately after intercourse; or during urination after intercourse
Self-image	Self-confidence; feelings about desirability, body, genitals, or sexual competence
Developmental history	Relationship with caregivers and siblings, traumas, loss of a loved one, abuse (emotional, physical, or sexual), consequences of expressing emotions as a child, cultural or religious restrictions
Past sexual experiences	Type (whether desired, coercive, abusive, or a combination), subjective experience (how rewarding, varied, and pleasing)
Personality factors	Ability to trust, comfort level with being vulnerable, suppressed anger causing suppression of sexual emotions, need to feel in control, unreasonable expectations of self, hypervigilance to self-harm (ie, worrying about pain that inhibits enjoyment), obsessiveness, anxiety, depressive tendencies, poor sexual self-image

STDs, sexually transmitted diseases.
From Porter R, ed. *The Merck Manual of Diagnosis and Therapy*. Whitehouse Station, NJ: Merck Sharp & Dohme; 2011. http://www.merckmanuals.com/professional/index.html. Accessed November 24, 2013.

FEMALE SEXUAL DYSFUNCTIONS

Female sexual dysfunction is common among women of all ages. The diagnostic criteria defining these disorders remain controversial. The various diagnoses are constantly being studied in an attempt to further refine them for the new edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*).[18] For better or for worse, *DSM* classifications are of utmost importance to providers because they influence, if not determine, insurance reimbursements for sexual health disorders or dysfunctions. The *DSM* and *International Classification of Diseases, Ninth Revision* (ICD-9) codes for these diagnoses may be found in the back of the *DSM* manual or via an online search for *DSM-5* diagnostic codes.

In the United States, it is estimated that 40% of women have sexual concerns and about 12% report distressing sexual problems.[19] Worldwide, about 40% of women report sexual complaints.[20]

In the Global Study of Sexual Attitudes and Behaviors, the most commonly reported dysfunctions were low libido or sexual drive (26 to 43%) and an inability to reach orgasm (18 to 41%).[20] The prevalence of sexual problems was highest in Southeast Asia and lowest in Northern Europe.

A key requirement in diagnosing female sexual dysfunction is that it creates personal distress for the woman, and many studies do not consider this nor do

they include women who are not in sexual relationships. One exception is the largest U.S. study of female sexual dysfunction, the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking survey (PRESIDE) that included over 30,000 women who responded to validated questionnaires and it included women who were not currently in a sexual relationship.[19] This study found that with or without personal distress, 43% of women reported at least one problem with sexual desire, arousal, or problems with orgasm. However, when asked about personal distress associated with the condition(s), only 22% of women reported personal distress and 12% attributed the distress to a specific type of sexual problem. Low levels of sexual desire was the most common sexual problem in respondents (39%), with orgasm difficulties only slightly less prevalent (21%); both were associated with distress in 5% of women.[19] The survey found that a poor self-assessment of health significantly correlated with distressing sexual problems for the participants.

In the PRESIDE study, the prevalence of sexual problems increased with advancing age, with the prevalence of distressing sexual problems being highest in women 45 to 64 years of age (15%), intermediate in women ages 18 to 44 years (11%), and lowest among women 65 years of age or older (9%).[19] These results are not consistent across all studies. For example, the National Health and Social Life Survey study of 1749 women ages 18 to 59 years who had a sexual partner in the last year found that apart from issues of vaginal lubrication, the prevalence of sexual problems tended to decrease with increasing age.[21]

The Challenge of Treatment

Female sexual disorders are often challenging to treat—even for practitioners specialized in the treatment of sexual dysfunction. Few medications exist that help to alleviate sexual dysfunctions, which can be frustrating for physicians as well as patients. In contrast, there are many medications that can interfere with sexual functioning. For example, approximately 30 million people are taking selective serotonin reuptake inhibitors (SSRIs), and it is estimated that about half of them experience alterations in their sexual behavior. Further, it is estimated that approximately half of this group will have persistent sexual issues even after they discontinue the medication.[22] Nonetheless, sexuality—including the lack of it—plays a profound role in many people's experience of life and their relationships.

For many women, the three major determinants of sexual dysfunction include relationship factors, medical issues, and life phases. Relationship factors, such as stress, financial issues, communication issues, etc., all impact sexuality. Physiologic issues or medical conditions such as diabetes, heart disease, cancer, or medication side effects, to name a few, need to be considered as well. Mental health conditions such as depression or anxiety, and often, the medications used to treat them may create or significantly contribute to sexual problems. Life phases that affect sexual functioning include pregnancy, child rearing, and menopause. These three general areas do not occur in a vacuum, which is why a biopsychosocial treatment model is imperative. "The biopsychosocial model provides a compelling reason for skepticism that any single intervention (i.e., a phosphodiesterase type 5 inhibitors, supraphysiological doses of a hormone, processing of childhood victimization, marital therapy, pharmacotherapy of depression) will be sufficient for most patients or couples experiencing sexual dysfunction."[23]

Many of the ways people cope and relieve stress have a negative impact on their sexual functioning, such as the following:

- Overreliance on substances including food, nicotine, and alcohol
- Overreliance on sedentary activity
- Avoidance of deeper emotions which include depression, anger, and passion
- Avoidance of vulnerability, maintaining tight control of mind and body

Use of biopsychosocial treatment approaches can help providers in their counseling of patients. These include sympathy and efforts to "normalize" the woman's concerns by letting her know how common sexual problems are. General health issues such as nutrition, exercise, sleep, and chemical dependence are always an aspect of sexual dysfunction treatment. Psychosocial issues such as mood and stress must be addressed because they are a huge contributing factor to any woman's sexual experience. The involvement of mental health professionals with expertise in sexuality and/or sex therapy is often helpful as well (Table 9.4).

TABLE 9.4 Outcome of Psychological Therapy for Arousal, Desire, and Orgasm Disorders: Wait List Controls

Mode of Treatment	Level of Efficacy
Marital and sex therapy plus/minus orgasm consistency training[a]	Significant improvements in arousal when sex therapy plus orgasm consistency given versus sex therapy alone
Behavioral and sex therapy, including modified sensate focus therapy	Approximately 60% show significant improvement
Cognitive behavioral therapy	50–74% show significant improvement
Directed masturbation and bibliotherapy	55–82% became orgasmic
Combination of CBT, sensate focus, and directed masturbation	Increased orgasmic response and initiation of sexual activity in majority

CBT, cognitive behavior therapy.
[a]Orgasm consistency training: encouragement of self-stimulation, sensate focus therapy with partner, and coital techniques to facilitate clitoral stimulation.
From Gibbs RS, Karlan BY, Haney AF, et al. *Danforth's Obstetrics and Gynecology*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

Other more concrete steps include the recommendation of books specific to the woman's concerns (individual recommendations are offered in an appendix to this chapter), encouraging her focus on enjoyment of the process of making love versus the goal of penile–vaginal intercourse or orgasm, and encouraging novel sexual activities both partners are willing to participate in as well as doing new activities with their partners as a means of sparking renewed interest in each other.

Similar to what is seen in men, female sexual dysfunction is related to the same risk factors as cardiovascular disease: smoking, hypertension, hyperlipidemia, and endothelial damage.[24] Women with hypertension may have decreased lubrication, orgasm, and increased sexual pain, whether the hypertension is treated or not; unfortunately, some antihypertensive drugs used for treatment may induce sexual dysfunctions in women as well.[25] Although studies are not consistent, there is some evidence that diabetes may also significantly impact the sexual health of women through neuropathy, endocrine changes, and vascular compromise.[26,27]

Depression, anxiety, and psychotic disorders are recognized risk factors for sexual disorders even without treatment.[28,29] Treatment for these conditions may exacerbate or induce sexual dysfunction, particularly antidepressants, which may cause low libido and difficulty with orgasm. Benzodiazepines, antipsychotic medications, and atypical antipsychotic medications may impact sexual function adversely.

Sexual complaints are common during the postpartum period although there is no evidence of long-term differences in sexual dysfunction between women who delivered vaginally and those who had a cesarean section.[30] There is no evidence that parous women have more sexual dysfunction than nonparous women.[19]

Pelvic organ prolapse and urinary incontinence are associated with sexual health issues, with 26 to 47% of women with urinary incontinence reporting sexual dysfunction.[31] In some reports, 11 to 45% of women experience urinary incontinence during intercourse, often with penetration or orgasm.[32,33] It is not surprising then, that in the PRESIDE study, urinary incontinence significantly correlated with distressing sexual problems.[19] The impact of surgical repair of pelvic floor disorders and sexual functioning is mixed, with some women reporting improvement and others reporting no change or new onset dyspareunia.[34,35]

In discussing sexual concerns with a woman, it is important to note any and all medications she may be taking; in some instances, it may be necessary to adjust or even change medication regimens to reduce sexual side effects—particularly antidepressants—because they are such a common contributor to sexual dysfunction. Other common medications that may interfere with sexual function include antihistamines, cardiovascular agents, antihypertensives, anxiolytics, and chemotherapy. Antihypertensives including thiazide diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors may interfere with normal vasocongestion of the genitals; out of these, thiazides are the most commonly implicated.[36] Anticholinergic drugs may decrease vaginal lubrication, whereas SSRIs may lead to diminished desire and problems with orgasm.

Progestin-only contraceptives do not appear to be associated with sexual dysfunction, whereas the effect of combined hormonal contraceptives on sexual health is controversial.[37] Although combined hormonal contraception suppresses testosterone levels through pituitary luteinizing hormone (LH) secretion, suppression, and an increase in sex hormone binding globulin, the correlation between this decrease in androgen activity and the sexual function of women using combined hormonal contraception is not clear cut. In fact, the use of exogenous androgens in oral contraceptive users does not appear to improve desire.

Substance use/abuse may also impede normal sexual functioning; alcohol is the most common agent. Other substances such as marijuana, cocaine, and heroine may also result in sexual dysfunction.

In order to establish the diagnosis of female sexual dysfunction, the sexual problem must not only be recurrent or persistent, it must also cause personal distress or interpersonal difficulty.[18] Sexual dysfunctions are categorized by the specific phase of the sexual response cycle they occur in, although in practice, many of the disorders are not limited to just one phase and more than one disorder may occur within the same patient. Because many of the female sexual dysfunctions will overlap, it is important to determine the primary disorder, that is, ask the patient what she believes is her primary sexual concern, and then note how any comorbid dysfunctions developed over time. For example, a patient may be concerned about her lack of desire to have sex, but further history taking reveals that she began to develop pain during sex and subsequently, her desire for it declined. In this instance, dyspareunia is the most likely primary dysfunction.

The American Psychiatric Association classification of female sexual disorders has six categories:

- Hypoactive sexual desire disorder
- Sexual aversion disorder
- Female sexual arousal disorder
- Female orgasmic disorder
- Dyspareunia
- Vaginismus[18]

When speaking with a woman who may have sexual dysfunction, it is clear that a complete medical and medication history must be obtained. The sexual history should include current sexual health problems, the nature of the problems, whether it is she or her partner who is having problems (or both), and whether they cause the patient any personal distress or interpersonal problems. Although a pelvic examination is strongly

TABLE 9.5 Physical Examination

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 Sjögren syndrome, 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 sclerosus, which may cause soreness with sexual stimulation. 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., pallor, friability, loss of elasticity, and moisture of vulval atrophy); lichen sclerosus; recurrent splitting of the posterior fourchette manifest as visible white lines perpendicular to fourchette edge; abnormalities of the hymen; 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); presence of cystocele, rectocele, 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 palpitation of the deep levator ani due to 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; pelvic tumor; fecal impaction as causes of deep dyspareunia; tenderness on palpitation of posterior bladder wall from anterior vaginal wall suggestive of bladder pathology.

Adapted from Massachusetts Medical Society. Basson R. Clinical practice. Sexual desire and arousal disorders in women. *New Engl J Med.* 2006;354:1497–1506.

recommended for patients with sexual pain, it should also be performed in patients with other sexual health complaints as well to confirm normal anatomy; evaluate for tenderness, masses, or lesions; look for prolapse or atrophy; and evaluate any concomitant gynecologic complaints that may, or may not, be related to the sexual dysfunction (Table 9.5).

Depending on the results of the history taking and/or physical examination, further laboratory testing may be warranted, for example, pelvic ultrasound, cervical cultures, thyroid-stimulating hormone (TSH), complete blood count (CBC), or prolactin levels. Androgen levels should not be measured as a means of determining the cause of a sexual problem because they are not an independent predictor of sexual function in women and the available assays for serum androgen levels in women are unreliable. The Endocrine Society Clinical Practice Guideline supports this approach and does not recommend diagnosing androgen deficiency in women because there is no well-defined clinical syndrome associated with this diagnosis, and there are no age-based normative data for serum testosterone and free testosterone concentrations in women.[38] Testing for estradiol or other estrogen levels or other sex steroids has no use in evaluating sexual complaints.

Hypoactive Sexual Desire Disorder

While acknowledging that there is no consensus about what is "normal" desire and that each woman will have her own definition based on her culture, background, sexual experience(s), and her own biologic drive, hypoactive sexual desire disorder (HSDD) is the most common sexual dysfunction among women, with a prevalence rate of approximately 22%.[1] HSDD is currently defined in the *DSM-5* as persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity.[18] Criticisms of this definition note that it considers sexual thoughts or fantasies to be a primary trigger for sexual behavior, but for women, the desire for sexual activity may be prompted by factors not addressed in the current definition, for example, wanting to experience tenderness, appreciation, or the feeling of desirability. Furthermore, the lack of sexual desire at the start of a sexual encounter does not necessarily indicate HSDD because some women may not feel a desire for sex initially but with sexual stimulation develop the desire. HSDD can be subdivided into a general lack of sexual desire or a situational one where the woman lacks desire for her current partner but still has desire for sexual stimulation either alone or with someone else. HSDD may be acquired, that is, it starts after a period of normal sexual function or it may be lifelong—the woman had always had low or no sexual desire.

The third International Consultation on Sexual Medicine (ICSM) recommended refining HSDD to directly reflect the fact that absence of desire in a woman does not necessarily equate with dysfunction.[39] It has been suggested that a lack of female desire is "inevitable" in long-term relationships and even in those partnerships considered healthy.[40,41] Research does demonstrate that women with low desire are frequently happy with their romantic relationship and not distressed about their low libido.[42] When the criteria of personal distress is taken into account, the prevalence of HSDD drops by about half.[43] It is possible that the lack of distress in some of these women is because they feel their situation is hopeless and they have essentially "given up" on their sex lives. It is not known if these women would admit distress if they believed their situation was able to be improved and they could feel sexual excitement again.

Because of its complex etiology, HSDD is perhaps the most difficult sexual concern to treat. Common concerns

TABLE 9.6 Etiologic Factors That Should Be Evaluated When Assessing Desire and Arousal Complaints in Women

	Predisposing Considerations	Precipitating Considerations	Maintaining Considerations
Biological	Endocrine factors, menstrual cycle disorders, history of surgery or medical illness, drug treatments affecting hormones or menstrual cycle, benign diseases	Change in hormonal status as a result of menopause, cancer, use of medications or drugs, current medical conditions	Drug treatment, metabolic/malignant disorders, other chronic medical conditions, hormone treatment
Psychosexual	Past sexual history (both positive and negative), unwanted sexual experiences, history of rape, violence, coercion, body image concerns/issues, personality traits and temperament (extroverted vs. introverted, inhibition vs. excitation), attachment history (past and present), coping resources, social/professional roles and responsibilities	Current relationship satisfaction; affective disorders (anxiety, depression); loss of loving feelings toward partner as a result of discovery of affair, deception, etc.	Anxiety, tension, communication problems
Contextual	Ethnic/religious/cultural messages, expectations, constraints; socioeconomic status/access to medical care and information; social support network	Relationship discord, life-stage stressors (divorce, separation), loss or death of close friends or family members, lack of access to medical/psychosocial treatment, economic difficulties, worries	Cultural myths

From Brotto LA, Bitzer J, Laan E, et al. Women's sexual desire and arousal disorders. *J Sex Med.* 2010;7(1, pt 2):586–614.

expressed by a woman with low desire include loss of pleasure in feeling feminine, a loss of physical and emotional intimacy with her partner, fear of her partner's infidelity, feelings of disconnection from her body, and feeling detached from sensual physical sensations. Many dynamics contribute to low desire in women, including physical, hormonal, emotional, spiritual, and partner variables (Table 9.6).

From a physical perspective, medications—such as antidepressants, oral contraceptives, antihistamines, antihypertensives, and diuretics—can negatively impact libido for some women. A woman who is tired and overworked may lose her interest in sex. A woman's disconnection from her physical self is an additional variable. In a fast-paced culture, people spend most of their time thinking rather than feeling. Tuning into sexual desire requires tuning into the body more generally and learning to feel pleasure in the body more generally as well. Lifestyle issues, such as poor sleep or inadequate nutrition, are also potential culprits. Emotions such as depression, anxiety, and stress are additional factors in HSDD.[43] Poor body image may cause diminished desire. When evaluating women with HSDD, interpersonal issues often need to be addressed as well. If a woman's lover is unskilled, or if her partner is a man with erectile dysfunction (ED) or premature ejaculation, or if the woman believes her sex life is rote and boring, a woman may lose her desire for sex. These issues are troubling for many women who do not want to hurt a partner's feelings with negative feedback about their sexual skills. Relationship conflicts and power struggles can also significantly weaken a woman's receptivity to sex. Relatedly, if she feels a spiritual void with her partner, she may be reluctant to open up to him sexually.

Regardless of how or why a woman's sex drive initially declines, both her mind and her body tend to be impacted over time. The Women's International Study of Health and Sexuality (WISHeS) study found that women with HSDD had large and statistically significant declines in health status, particularly in mental health, social functioning, vitality, and emotional role fulfillment.[44] Others have found that women with HSDD have more comorbid medical conditions and are twice as likely to report fatigue, depression, issues with memory, back pain, and a lower quality of life.[45]

A woman's medical conditions may influence her risk for HSDD, but assuming that a biomedical approach alone will best serve the patient for treatment purposes is not recommended. The biopsychosocial treatment model includes biological, psychological, and social/interpersonal components in its approach and places less pressure on the physician to offer a single solution to such a complex problem. It is imperative that a woman expects to play a significant role in her own treatment rather than waiting for her physician to "heal" her because the patient will probably be disappointed by the latter option. "It is up to the patient to take the risks involved in deepening her sense of connection to her own body and to her partner. The patient must be willing to experiment with her sensual expression, open to feelings of joy and vulnerability with her partner, and let go of control to her partner. She must get adequate sleep and proper nutrition for her body to respond sexually."[46] Thus, HSDD treatment involves a cooperative effort between physician and patient. Many clinicians believe they do not have the tools or the skills to screen or assess patients for HSDD. There are several screening tools available that are easy to use. One example is the Decreased Sexual Desire Screener (DSDS) that is done with the patient. It starts with four questions and if the patient answers "yes" to all of the questions, they continue to the fifth question that has seven parts

(Table 9.7). If the patient is identified as having HSDD, the clinician may choose to employ the PLISSIT model (Fig. 9.3). This model has four steps: permission, limited information, specific suggestions, and intensive therapy. The first step validates the patient's concerns and makes clear that sexual problems such as HSDD are real and very prevalent. The second step provides basic education to the patient about the sexual response cycle, the components of desire, and possible resources and tools that further discuss the patient's sexual concerns. In the third step, the clinician may offer suggestions to help improve her desire levels. The final step is often beyond the scope of most clinician's expertise and involves referral to a specialist in sexual medicine.

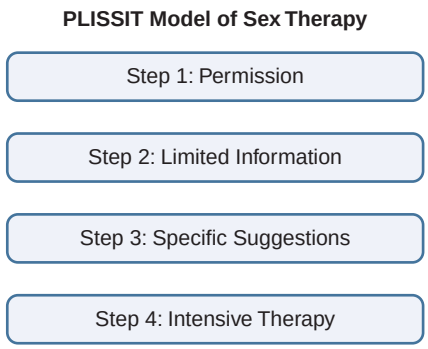

FIGURE 9.3 PLISSIT model of sex therapy. (Adapted from Annon JS. The PLISSIT model: a proposed conceptual scheme for the behavioral treatment of sexual problems. *J Sex Educ Ther*. 1976;2[2]:1–15.)

TABLE 9.7 The Decreased Sexual Desire Screener Used in the Nontreatment Validation Study

Dear Patient, *Please answer each of the following questions:*

1. In the past, was your level of sexual desire or interest good and satisfying to you?	Yes/No
2. Has there been a decrease in your level of sexual desire or interest?	Yes/No
3. Are you bothered by your decreased level of sexual desire or interest?	Yes/No
4. Would you like your level of sexual desire or interest to increase?	Yes/No
5. Please check all the factors that you feel may be contributing to your current decrease in sexual desire or interest.	
A: An operation, depression, injuries, or other medical condition	Yes/No
B: Medication, drugs, or alcohol you are currently taking	Yes/No
C: Pregnancy, recent childbirth, menopausal symptoms	Yes/No
D: Other sexual issues you may be having (pain, decreased arousal or orgasm)	Yes/No
E: Your partner's sexual problems	Yes/No
F: Dissatisfaction with your relationship or partner	Yes/No
G: Stress or fatigue	Yes/No

When complete, please give this form back to your clinician.

Clinician: ***Verify with the patient each of the answers she has given.*** The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, characterizes hypoactive sexual desire disorder (HSDD) as a deficiency or absence of sexual fantasies and desire for sexual activity, which causes marked distress or interpersonal difficulty and which is not better accounted for by a medical, substance-related, psychiatric, or other sexual condition. HSDD can be either generalized (not limited to certain types of stimulation, situations, or partners) or situational and can be either acquired (develops only after a period of normal functioning) or lifelong. If the patient answers "NO" to any of the questions 1 through 4, then she does not qualify for the diagnosis of generalized acquired HSDD. If the patient answers "YES" to all of the questions 1 through 4 and your review confirms "NO" answers to all of the factors in question 5, then she does qualify for the diagnosis of generalized acquired HSDD. If the patient answers "YES" to all of the questions 1 through 4 and "YES" to any of the factors in question 5, then decide if the answers to question 5 indicate a primary diagnosis other than generalized acquired HSDD. Comorbid conditions such as arousal or orgasmic disorder do not rule out a concurrent diagnosis of HSDD. **Based on the above, does the patient have generalized acquired hypoactive sexual desire disorder? ____YES ____NO**

From Clayton AH, Goldfischer ER, Goldstein I, et al. Validation of the decreased sexual desire disorder (DSDS): a brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). *J Sex Med*. 2009;6(3):730–738.

Sex therapy is brief cognitive behavioral psychotherapy that specifically focuses on sexual concerns; it tends to be short term (5 to 20 visits) and is solution focused. In some instances, referral to a mental health specialist to address other issues or concerns not specifically related to sex may also be helpful for the patient.

There are no FDA-approved pharmacologic treatments for women's sexual dysfunction at this writing. Nonetheless, some women find benefit from testosterone supplementation in the treatment of low desire.[47] Challenges to the use of testosterone therapy involve the fact that testosterone assays in this country are male-based and not sensitive enough for women who occupy the lower 10% of those levels. Obviously, it is also challenging to use supplementation intended for men on females. Practitioners are thus forced to use off-label or compounded products, often as an empiric trial after ruling out other causes for low desire. Off-label treatment with testosterone supplementation is controversial, particularly for premenopausal patients. There is a lack of agreement regarding normative ranges for women, as well as no standard formulation for systemic androgen replacement.[48,49] Some practitioners, as well as the Endocrine Society, do not recommend testosterone therapy because of the lack of diagnostic levels indicating testosterone insufficiency and the lack of long-term safety data,[50] especially with respect to heart disease and breast cancer. Studies have shown mixed results with regards to testosterone in vivo decreasing or increasing breast cell proliferation.[51,52] In one study, testosterone in vitro was shown to decrease breast cell proliferation.[53] However, many questions remain, for example, does testosterone directly improve libido or is it aromatization to estrogen, and does testosterone work on sex drive directly or indirectly via mood?

Conservative guidelines for practitioners who administer off-label testosterone therapy have made some general, conservative recommendations during testosterone use. For example, according to Basson et al.,[54]

> . . . the testosterone patch appears to be effective in the short term in postmenopausal women with

HSDD. Achieving physiological testosterone levels by transdermal delivery minimizes adverse effects. Relative contraindications include androgenic alopecia, acne, hirsutism hyperlipidemia, and liver dysfunction. Absolute contraindications include presence or high risk breast cancer, endometrial cancer, venothrombotic episodes, cardiovascular disease. Monitoring should include annual breast and pelvic examinations, annual mammography, evaluation of abnormal bleeding, evaluation for acne, hirsutism, and androgenic alopecia. Monitor testosterone by mass spectrometry (sex hormone binding globulin, calculated free T) with goal of not exceeding normal values. Consider lipid profile, liver function tests, complete blood count. Use for more than 6 months is contingent on clear improvement and absence of adverse effects.

Any discussion about the use of androgen therapy, in any form, must include a full explanation of all potential benefits and risks. Women considering androgen therapy must understand that the data on safety and efficacy is very limited, and this includes data on long-term use, either with or without estrogen therapy (ET). They should also be aware that none of the commonly used androgen therapies are approved by the FDA for treating HSDD because of the limited clinical trial data as well as the concerns about long-term safety. This discussion should be carefully documented in the patient's records.

Testosterone is the most commonly used androgen treatment for female sexual dysfunction, particularly HSDD. In randomized trials and systematic reviews where it was used with estrogen (with or without progestin)—it has been in postmenopausal women—it did show an improvement in sexual function.[55–58] The formulations and delivery methods vary across studies, although the largest series of controlled clinical trials used a transdermal testosterone patch that delivered 300 mcg/day of testosterone in postmenopausal women with HSDD.[56,58] Most of the studies included postmenopausal women who were on concurrent ET, although one large trial found similar results in women not using estrogen/progestin treatment.[59] Data on the use of androgen treatment in premenopausal women are scant and inconclusive, and the inadvertent exposure of a developing fetus is a significant potential risk to be considered.[60,61]

In Europe, the Intrinsa 300 mcg testosterone patch is approved for use in female sexual dysfunction; it is applied twice weekly. Despite the lack of FDA-approved androgen therapies in the United States, products that are used include methyltestosterone, compounded micronized testosterone, compounded testosterone ointments or creams (1 or 2%, use 0.5 g every day applied to the skin on the arms, legs, or abdomen), and testosterone patches or gels formulated for hypogonadal men. Cutting patches is not advised because there is no data available on product stability or the resulting testosterone levels. Gels are difficult to use because the amount needed would be approximately 1/10th the dose prescribed for men, and this is very hard to accurately gauge with gels in pumps or packets. There have been FDA reports of adverse events due to secondary exposure of children to the skin of adults who recently applied topical testosterone. Use of oral formulations may result in adverse changes in liver enzymes or lipid levels because of the first-pass hepatic metabolism.

Flibanserin is a 5-hydroxytryptamine $(5\text{-HT})_{1A}$ agonist and 5-HT_{2A} antagonist, which reduces the inhibitory effect of serotonin on dopamine and norepinephrine. It is a nonhormonal, centrally acting agent, which went before FDA review after completion of its phase III clinical trials in 2010, but it was not approved, in large part because the absence of long-term treatment data made it difficult to evaluate effectively.

Although there was hope initially that phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil would be beneficial in women with female sexual dysfunction, studies reported inconsistent results.[62–64] There is some evidence that sildenafil may have good results on sexual arousal and orgasm in premenopausal women with SSRI-associated sexual dysfunction.[65] However, there was no change in sexual desire for women in this study.

There is some evidence that bupropion, 150 mg twice a day or sustained release 300 mg/day, may increase sexual desire, arousal, and orgasm compared to placebo, but more trials are clearly needed.[66,67]

Sexual Aversion Disorder

Sexual aversion disorder (SAD) is defined by the *DSM-5* as a persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a partner, which causes distress or interpersonal difficulty. These patients steer clear of sex at all costs. In SAD, the scope of sexual stimuli that produce the aversion range from a specific act or aspect of the sexual encounter (e.g., direct genital contact) to any and all sexual stimuli (including kissing and embracing). Given that a core feature of the human condition is sexuality, the impact of any sexual phobia or aversion can be quite profound. SAD may be lifelong or acquired, generalized or situational, and may be due to psychological or combined factors.

In a sexual situation, a patient with SAD may have panic attacks or other severe anxiety symptoms. In fact, critics of this diagnosis suggest that it may be more appropriately classified as an anxiety disorder rather than a sexual disorder.[68] In addition to anxiety, patients may report emotions such as fear, revulsion, or disgust at the thought of sexual contact.

Relative to the research done on HSDD, much less is known about the prevalence, etiology, and treatment of SAD. SAD is actually rarely researched and there is some question of whether it should even be included in the new edition of the *DSM*.[69] There are no published longitudinal studies investigating the etiology of SAD so proposed mechanisms are based on theory or conjecture

alone. There are no published data on treatment(s) or treatment efficacy for SAD in men. There are two published case studies of the effective use of systematic desensitization in women with SAD, a treatment approach that is known to work with other anxiety disorders.[70–72]

Although SAD is one of the two sexual desire disorders with HSDD being the other, there are few similarities between the two. There is some overlap with HSDD and vaginismus, defined as recurrent or persistent involuntary vaginal muscle spasm. Because many women with vaginismus are fearful of (painful) vaginal penetration, this often results in avoidance behavior and in severe cases, aversion. Some cases of aversion may actually be due to vaginismus, although it is possible to have both disorders coexist.

Treatment of SAD is generally emotionally focused and involves a sex therapist. However, a gynecologist must first rule out a pain disorder or other physiologic variables that could interfere with a woman's sexual response.

Sexual Arousal Disorder

Female sexual arousal disorder (FSAD) is defined as "the persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement."[18] Some women describe this sensation as being sexually "dead" or "numb" in that the body does not respond to sexual stimulation. The prevalence of FSAD is approximately 14%.[1] However, this diagnosis is becoming controversial because it rests on the genital response of vascular engorgement and lubrication of the vagina by definition. In clinical practice, women seldom complain of specific genital arousal issues. Instead, they may allude to arousal difficulties by noting pain during intercourse or reduced feelings of arousal. It is important to recognize that having reduced or simply lacking feelings of sexual pleasure or enjoyment is not sufficient to make the diagnosis of an arousal disorder. This strict focus on the genital response ignores the fact that sexual arousal is composed of both subjective components and physical genital components. Yet, research consistently demonstrates that women are poor at accurately identifying their state of physiologic sexual arousal. Women's subjective reports of arousal do not correlate well to their vaginal vasocongestion[73]—Their physiologic response can occur independent of their subjective sense of being "turned on." For many women, feelings of sexual arousal are determined to a larger extent by the situational context than by the strength of their genital response. Because HSDD is often seen in combination with arousal problems, some researchers suggest that FSAD be combined with HSDD in the *DSM-5* as Sexual Interest/Arousal Disorder[74] (Fig. 9.4).

As with other sexual disorders, consideration must be given to the effect(s) of chronic diseases on sexual functioning. For example, there is evidence that the genital response is diminished in women with spinal cord injury, nerve damage due to oncologic surgery to the uterus, and women with diabetes mellitus.[75–77] Drugs that act on neurotransmitter systems such as antidepressives (SSRIs) and antipsychotics (dopamine antagonists) may have negative effects on sexual arousal.[78]

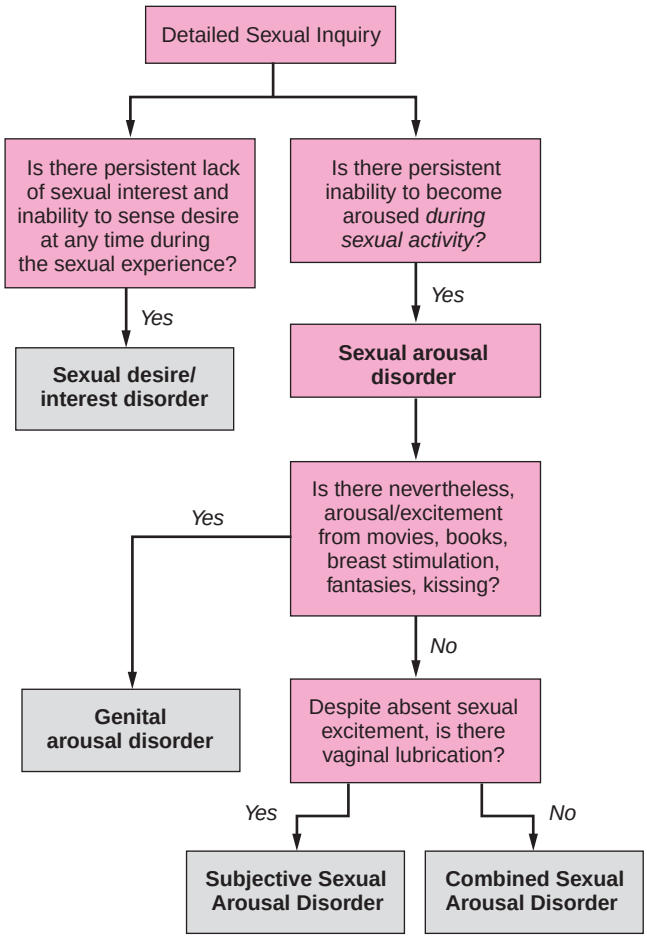

FIGURE 9.4 Algorithm to identify the subtype of arousal disorder. (From Gibbs RS, Karlan BY, Haney AF, et al. *Danforth's Obstetrics and Gynecology*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.)

Arousal disorder can be challenging for a physician to treat. Some researchers suggest that the heterogeneity of this disorder hinders the identification of effective treatment options. For example, so many intrapersonal and interpersonal issues can result in decreased lubrication that a woman may believe she has a physiologic dysfunction when in fact her lack of arousal is due to anger at her partner, inadequate foreplay, or self-consciousness about her body. For healthy women with arousal problems, the mechanism of classical conditioning may be involved.[79,80] In laboratory studies on women, the sexual arousal response to a specific stimulus can be positively conditioned by repeatedly pairing the stimulus with pleasurable sexual stimulation. If a woman has had very little rewarding sexual experiences, the paucity of positive associations may result in few stimuli that can elicit sexual desire and arousal. Sexual stimuli can also lose

their attractiveness when sex repeatedly results in negative outcomes, for example, anxiety, disappointment, or pain; sexual stimuli lose their attractiveness resulting in a suppressed sexual arousal response along with a reduction in any subjective pleasure from the stimuli.[81] Recently, a laboratory study showed that when an erotic stimulus was repeatedly followed by a pain stimulus, this suppressed the sexual arousal response and the subjective appreciation of the erotic stimulus.[79]

In general, the same-sex therapy and cognitive interventions are used for both arousal problems and problems of low desire. With arousal difficulties, there may be an increased focus on masturbation, with the aim of teaching the woman and the couple step by step how to achieve adequate erotic stimulation.[82] Most sex therapy is composed of sex education, a defined period of coitus prohibition, and subsequently, several successive so-called sensate focus exercises. These exercises are used to help diminish spectator behavior, decrease performance-targeted behavior, and help recognize and address any cognitive thought processes and expectations that may undermine arousal and/or desire. Other interventions may include exercises that encourage the identification of sexual stimuli or that help the woman reach orgasm, such as masturbation exercises for women and coital techniques that allow for optimal clitoral stimulation. Patients are often encouraged to experiment with store-bought lubrication; extending foreplay time; and identifying creative ways to increase their arousal both before and during sex with fantasy, sex toys, or new sexual scripts (Table 9.8).

Cognitive restructuring aims at thoughts that can inhibit sexual desire and arousal, such as negative self-esteem, thought processes, or expectations, which lead to restricted physical intimacy or sexual initiative (e.g., "If I kiss him, it will have to lead to intercourse") and

TABLE 9.8 Types of Lubrication

Petroleum-Based Lubricants

Examples: petroleum jelly (Vaseline), mineral oil, massage oil

Pros: Inexpensive, easily accessible, safe for the rectum and will not destroy condoms, dental dams and gloves made from polyurethane or nitrile-based materials.

Cons: Can irritate the vagina, cause vaginal infections, destroy latex condoms, dental dams and gloves, and stains fabric.

Natural Oil-Based Lubricants

Examples: vegetable oil, olive oil, Crisco, coconut oil

Pros: Safe to ingest, inexpensive, easily accessible and will not destroy polyurethane or nitrile-based condoms, dental dams and gloves.

Cons: Can destroy latex condoms, dental dams and gloves and stain fabric; can be confused by patients with petroleum-based lubricants, thus leading to irritation in the vagina and of the vulva.

Water-Based Lubricants With Glycerin

Examples: Astroglide, KY (Liquid/Jelly), Wet

Pros: Widespread distribution (available in nearly every major drugstore) and are the most commonly recommended and recognized; inexpensive, do not stain fabrics and are safe to use with all condoms, dental dams and gloves.

Cons: Can dry out quickly, often becoming sticky or tacky; are suspected to increase the risk of yeast infections in women who are prone to them, and often contain parabens that can be irritating to the sensitive genital skin; may have potential to increase risk of HIV transmission.

Glycerin-Free Water-Based Lubricants

Examples: Liquid Silk, Slippery Stuff, carrageenan, Sliquid, Good Clean Love

Pros: Last longer than lubricants with glycerin, and can reduce irritation to the genitals; do not stain fabric and are safe to use with all latex condoms, dental dams and gloves.

Cons: Can have a bitter taste due to the absence of glycerin; may be difficult to locate unless a patient seeks out adults-only boutiques or online retailers; may contain parabens.

Silicone Lubricants

Examples: Eros, Wet Platinum, Pink, Gun Oil, KY Intrigue, Liquibeads

Pros: Hypoallergenic and suitable for sensitive genitals; safe for use with all condoms, dental dams and gloves (except for items themselves made of silicone); waterproof, odorless, tasteless and longer lasting than water-based lubricants; not found to increase risk of HIV transmission.

Cons: Expensive, relatively difficult to locate and must be washed off with soap and water; extremely flammable.

Warming and Stimulating Lubricants

Examples: KY Yours and Mine, Sliquid Organics O Gel, System Jo Silicone Warming and Emerita Response Cream

Pros: May provide extra lubrication and increased sensation

Cons: May cause burning sensation and irritation

Desensitizing Lubricants or Gels

Examples: Moist anal lube, Anal Eaze

Pros: Contain numbing agents such as lidocaine or benzocaine; reduce pain with anal penetration

Cons: Woman may not notice any tearing that may be happening during sex; tears and fissures (even small ones) increase the risk of transmission of infections, development of wounds and fissures and possible long-term damage to the anatomy of the anal area.

Creams or Lubricants Containing L-Arginine

Examples: Daisy, HerSolution Gel

Pros: may increase blood circulation in the sexual organs

Cons: While evidence is lacking, there is concern these may stimulate genital herpes outbreaks in people already infected with genital herpes

Lubricants With Parabens

Examples: methylparaben, propylparaben and butylparaben.

Pros: Help deter microbial growth in many lubricants and other personal care products.

Cons: May cause allergic reactions

Lubricants and Fertility

There is only one lubricant (*Pre-Seed*) that has been shown not to interfere with conception. Even the water-soluble lubricants containing no spermicides may have negative effects on sperm motility

Lubricants and STI Transmission Risk

Certain lubricants may increase the transmission of HIV and other STIs. Water-based lubricants with glycerin

Used during anal sex showed more adverse effects than other water-based lubricants, oil-based lubricants, and silicone-based lubricants.

STI, sexually transmitted infection.

From Russo J, Rohan LC, Moncla B, et al. Safety and anti-HIV activity of over-the-counter lubricant gels. Presented at: International Microbicides Conference; May 25, 2010; Pittsburgh, PA; Andelloux M. Products for sexual lubrication: understanding and addressing options with your patients. *Nurs Womens Health.* 2011;15(3):253–257.

negative expectations about one's own sexual response. The use of partner therapeutic interventions may help to promote positive intimate experiences, improve communication, address negative emotions, and allow for a constructive negotiation of wishes and desires. Communication exercises can be general or specifically aimed at communication about sexuality.

Pharmacologic options for treating arousal disorder are very limited. PDE5 inhibitors have been explored as an off-label treatment option but thus far have been used with mixed results.[83] In addition, off-label use of bupropion has had some success in improving arousal in a population of women with HSDD.[84] In postmenopausal women, estrogen supplementation may increase vaginal blood flow, making sex more pleasurable and ultimately lead to a cycle of more sex and decreased arousal difficulties. Without estrogen, the vagina has far less capability of vasocongestion resulting in diminished lubrication and genital arousal. It is suggested that local estrogen is insufficient for this response and systemic estrogen is more effective at increasing vaginal blood flow.[85]

A newly identified disorder, persistent genital arousal disorder (PGAD), represents the inverse of the arousal continuum—too much arousal. These patients feel that they cannot "turn off" their genital arousal, even in the absence of conscious sexual desire.

> There is spontaneous, intrusive and unwanted genital arousal, e.g., tingling, throbbing, and pulsating, in the absence of sexual interest and desire. Any awareness of subjective arousal is typically but not invariably unpleasant. The arousal is unrelieved by one or more orgasms and the feelings of arousal persist for hours or days.[48]

It is currently being considered for inclusion into the *DSM-5*.

It is suggested that PGAD is relatively unknown because patients have been too embarrassed to discuss their symptoms with their physician. The following etiologies for PGAD have been suggested: central and/or peripheral neurologic changes (head injuries, specific brain lesion anomalies, seizure disorders, pelvic or pudendal nerve hypersensitivity or entrapment), medications (initiation or discontinuation of SSRIs or serotonin and norepinephrine reuptake inhibitors [SNRIs] or other pharmaceutical or over-the-counter products), psychological vulnerabilities (e.g., past history of sexual abuse, major stress), or some combination of all three.[86] Because of the wide variability in etiology, a variety of treatments have been suggested, including pelvic massage, cognitive behavioral therapy for management of discomfort and support, and perhaps mood-stabilizing or antiseizure medications.[86]

Female Orgasmic Disorder

Female orgasmic disorder (FOD) is defined as persistent delay in, or absence of, orgasm following a normal sexual excitement phase that causes personal distress or interpersonal difficulty.[18] One commonly cited study found orgasmic problems to be the second most common sexual dysfunction in women, with 24% of women experiencing orgasm concerns within the past year.[1] The diagnosis of FOD should be based on the clinician's judgment that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives. This can be challenging because women exhibit wide variability in the type of intensity of stimulation that triggers orgasm. Further, there is no objective "marker" of when orgasm occurs in women. Primary orgasmic disorder means that a woman has never reached orgasm. Women have secondary orgasmic disorder when they can reach orgasm either infrequently, alone but not with their partner, or they require a specific, restricted condition in order to orgasm. Secondary orgasmic disorder is more common and usually more challenging to treat.

The diagnosis of orgasmic disorder rests largely on subjective or self-reporting yet subjective descriptions of orgasm strongly suggest that it is experienced in different ways both across individuals and on different occasions by the same individual.[87] Many women require clitoral stimulation to reach orgasm, and only a relatively small proportion report that they always experience orgasm during intercourse. One area of longstanding controversy is the Gräfenberg, or "G" spot, an area of heightened erotic sensitivity in the anterior wall of the vagina. It has been proposed that there are three "erogenous sites" in this area of the vagina and they comprise an "anterior wall erogenous complex."[88] In a recent study using ultrasound of the clitoris, one possible mechanism for the increased sensitivity of this area may be explained by pressure and movement of the clitoris root during sexual activity.[89] The proportion of women who experience localized erotic sensitivity in this area is not well known.

The etiology of FOD tends to be multifactorial because it relates to genetics, medical conditions, medications, alcohol and drug use, other sexual dysfunctions, mental illness, life stressors, communication deficits, and relationship issues. In most cases, the etiology remains uncertain. Although a wide range of psychological factors, such as anxiety, impact a women's ability to reach orgasm, there is a great deal of variability across women in how likely they are affected by, or to what extent they are affected by such factors. The *DSM-5* text includes this statement: "No association has been found between specific patterns of personality traits or psychopathology and orgasmic dysfunction in females."[18] In one review of the literature, the authors found no support for associations between female orgasm response and psychopathologic adjustment.[90] Efforts to find relationships between orgasmic problems and specific sociodemographic factors have yielded inconsistent findings. The most consistent relationships

between orgasmic difficulties are found in women with poor physical and mental health as well as relationship difficulties or partner-related variables.[91–93] Not surprisingly, this finding is true for most sexual problems in women.

Several types of medication may interfere with sexual function, including orgasm. For SSRIs, the most commonly reported side effect is delayed orgasm in both men and women. Estimates are that between 30 and 60% of those using these medications are affected.[94] Women may be more susceptible to the orgasm-related side effects of SSRIs than men.

Treatment for orgasmic disorders depends on the patient's unique needs. Kegel exercises have traditionally been advocated as part of treatment, although more recently, the efficacy of this approach has been questioned.[95] For primary anorgasmia, regularly scheduled masturbation is usually effective.[96] In addition, pelvic floor physical therapy can help a woman release tension in her pelvic floor that prevents her from relaxing. If a woman is postmenopausal, estrogen can help increase pelvic blood flow, which can intensify sensation and support orgasm. Treatment of secondary orgasmic disorder depends on the patient's particular concerns. Research demonstrates that some women who struggle to orgasm during intercourse find the coital alignment technique helpful.[97] This is a method of intercourse involving more superficial thrusting where the man's body also rubs against the woman's clitoris.

Treatment of orgasm problems with medication has been minimally effective. Some women do find orgasm becomes easier with off-label use of the antidepressant bupropion.[98] The efficacy of PDE5 inhibitors with women has been modest, although for women suffering delayed orgasm due to SSRI use, one placebo-controlled study reported that sildenafil treatment improved symptoms of delayed orgasm in women.[65,99]

Sexual Pain Disorders

Sexual pain disorders are extraordinarily complex multisystemic and multifactorial dysfunctions that are hard to quantify and oftentimes even harder to treat.[100] Sexual pain disorders may occur in both men and women but it is much more common in women. There are two sexual pain disorders listed in the *DSM-5*: dyspareunia and vaginismus. In some categorizations of sexual pain, a noncoital sexual pain disorder is recognized as recurrent or persistent genital pain that is induced by noncoital sexual stimulation.[101] Sexual pain disorders may be primary or secondary; they may occur with each sexual experience or in specific situations or contexts. Sexual pain may be nociceptive and/or neuropathic in nature. Nociceptive pain is related to ongoing disease or injury due to tissue damage. Neuropathic pain results from abnormal neural activity that may have originally resulted from nerve injury but it persists even if the injury or disease process affecting the nerve(s) is no longer occurring. In the vulva, nociceptive pain may become neuropathic when there is injury to peripheral nerves, the spinal cord, or the brain.[102] The vestibule is the site of sexual pain for many women and is sensitive to both touch and temperature. The most sensitive portion of the vagina is the area that is contiguous with the vestibule, and the distal vagina has more pain fibers than the proximal vagina.

Dyspareunia is recurrent or persistent genital pain associated with sexual intercourse. The pain may be felt at the point of entry in the vagina, deep within the vagina, or associated with the back and forth movements during intercourse. Painful sex may be caused by medical issues, such as inflammation, infection, vaginal dryness, or injury to the vulva. Medications may also be an etiology for dyspareunia (Table 9.9). It can also be caused by psychological issues, such as emotional stress, fear of intercourse, or a history of sexual trauma. Although a traumatic instance or repeated instances may lead to pain during sex, it is important not to overestimate the link between painful sex and sexual abuse (Table 9.10). Prevalence rates of dyspareunia vary significantly and generally range from 6.5 to 45% in older women and 14 to 34% in younger women.[103]

Vaginismus is defined as a recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress or interpersonal difficulties. These spasms close the vagina and thus make sexual intercourse painful if not impossible. Recent research, however, has shown that vaginal muscle spasm is not a reliable or valid indicator of vaginismus.[104] It has been proposed that vaginismus be reframed as a condition where there are persistent difficulties in allowing vaginal entry of a penis, finger, and/or any object, despite the woman's expressed desire to do so.[105] This reconceptualization shifts attention from a specific muscle spasm to a description that encompasses the patient's subjective experience and behavioral factors associated with vaginismus. Women with vaginismus often develop anxiety symptoms that impede their sexual function.[100] They may report a variety of sexual concerns such as the belief that sex is sinful or offensive, an aversion to a man's penis or to men in general, fears about pregnancy or childbirth, fears that sex will be painful, lack of anatomic awareness, homoerotic feelings, or dislike of semen.[106] For some women, the physiologic, cognitive, and behavioral factors of vaginismus may interact in a cyclical fashion that both causes and maintains the condition.[107] Prevalence rates for vaginismus are speculative because of a lack of epidemiologically sound research, but estimates range from approximately 12 to 17%.[108]

Differentiating between dyspareunia and vaginismus is extremely difficult to do in clinical practice. There is a lot of overlap in their clinical presentations. Adding

TABLE 9.9 Medications Associated With Dyspareunia

Category or Mechanism	Specific Medications or Classes of Medications	Comment
Medications that may induce vulvovaginal atrophy	• Aromatase inhibitors • Gonadotropin-releasing hormone agonists or antagonists • Some chemotherapeutic agents • Tamoxifen • Depot medroxyprogesterone acetate	If menopause is induced, vaginal atrophy will result. If the effect is temporary, these changes will reverse when the medication is discontinued. Some chemotherapeutic agents result in premature ovarian failure. In premenopausal women, tamoxifen has an anti-estrogenic effect on the vaginal epithelium, resulting in atrophy.[a] In contrast, in postmenopausal women, tamoxifen has an estrogenic effect on the vaginal epithelium. This results in increased vaginal discharge. Some postmenopausal women who are taking tamoxifen develop recurrent candidal vulvovaginitis, with resultant dyspareunia. Depot medroxyprogesterone acetate suppresses the hypothalamic-pituitary axis, which induces hypoestrogenism and vaginal atrophy.
Oral contraceptives		Some data suggest that oral contraceptives are associated with vestibulodynia. The mechanism of this is unclear.[b] These findings have not been investigated for other formulations of estrogen-progestin contraceptives (patch, vaginal ring).
Anticholinergics	• Anti-histamines (eg, diphenhydramine, chlorpheniramine) • Amitriptyline	May result in vaginal dryness and dyspareunia.
Medications that increase the risk of recurrent candidal vulvovaginitis	• Immunosuppressants (eg, glucocorticoids, TNF-alpha inhibitors) • Antibiotics	Candidal vulvovaginitis is associated with the development of vulvodynia.
Topical agents that cause irritant or allergic reactions	• Spermicides	
Medications that may result in painful clitoral tumescence[c–i]	• Serotonergic agents (citalopram, nefazodone, trazodone) • Dopaminergic agents (bupropion, bromocriptine, olanzapine)	
Antihypertensives		Sexual dysfunction appears to occur more frequently in hypertensive women. It is unclear whether this is associated with the hypertension itself or with antihypertensive medications.

[a]Stewart EG. Approach to the women with sexual pain. UpToDate Web site. http://www.uptodate.com/contents/approach-to-the-woman-with-sexual-pain#subscribeMessage. Accessed November 24, 2013; with data from Mourits MJ, De Vries EG, Willemse PH, et al. Tamoxifen treatment and gynecologic side effects: a review. *Obstet Gynecol.* 2001;97:855.
[b]Goldstein A, Burrows L, Goldstein I. Can oral contraceptives cause vestibulodynia? *J Sex Med.* 2010;7:1585.
[c]Berk M, Acton M. Citalopram-associated clitoral priapism: a case series. *Int Clin Psychopharmacol.* 1997;12:121.
[d]Brodie-Meijer CC, Diemont WL, Buijs PJ. Nefazodone-induced clitoral priapism. *Int Clin Psychopharmacol.* 1999;14:257.
[e]Battaglia C, Venturoli S. Persistent genital arousal disorder and trazodone. Morphometric and vascular modifications of the clitoris. A case report. *J Sex Med.* 2009;6:2896.
[f]Pescatori ES, Engelman JC, Davis G, et al. Priapism of the clitoris: a case report following trazodone use. *J Urol.* 1993;149:1557.
[g]Levenson JL. Priapism associated with bupropion treatment. *Am J Psychiatry.* 1995;152:813.
[h]Blin O, Schwertschlag US, Serratrice G. Painful clitoral tumescence during bromocriptine therapy. *Lancet.* 1991;337(8751):1231.
[i]Sevincok L, Topaloglu B, Kiviloglu N. Neurologic soft signs and olanzapine treatment in chronic schizophrenia. *J Clin Psychopharmacol.* 2004;24:571.

to the diagnostic complexity is that these disorders can co-occur. There is a proposal to remove these two specific disorders in the new edition of the *DSM* and instead use the term Genito-Pelvic Pain/Penetration Disorder. Accurate diagnosis of sexual pain disorders is further challenged by additional medical conditions that present with pelvic pain. For example, provoked vestibulodynia (PVD), or what was recently known as vulvar vestibulitis syndrome, presents with "severe pain on vestibular touch or attempted vaginal entry, tenderness to pressure localized within the vulvar vestibule, and physical findings confined to vestibular erythema of various degrees."[109] The term PVD now encompasses disorders previously referred to as vulvodynia, clitorodynia, vulvar vestibulitis, provoked/unprovoked/generalized/localized vestibulodynia, and pelvic pain, among others. However, these terms are still being used in the literature, and confusion about these diagnoses unfortunately remains.

Research estimates that 3 to 7% of reproductive-aged women suffer from vulval discomfort, also referred to as vulvodynia.[110] The pain from these disorders is not necessarily related to sexual intercourse, which is what distinguishes them from the sexual pain disorders in the *DSM-5*. Although vulvodynia and the related disorders are not classified as sexual dysfunctions, knowledge of them is required to accurately diagnose the sexual pain disorders. More information on vulvodynia and related disorders may be found in the Chapter 7, Chronic Pelvic Pain, and Chapter 14, Benign Disorders of the Vulva and Vagina, and patients with vulvodynia may contact the National Vulvodynia Association (www.nva.org) for more information as well.

It is common for women with vulvodynia or a sexual pain disorder to have pain for many years before being accurately diagnosed. As a result, these patients are often emotionally distressed, and they should be assessed for depression and anxiety disorders.[111] They

TABLE 9.10 Subtypes of Chronic Dyspareunia in Women

Medical Disorder	Type of Dyspareunia	Findings on Physical Examination	Therapeutic Options and General Comments
Vulvovaginal atrophy: associated with renal failure, chemotherapy-induced menopause, hypothalamic or pituitary disease, bilateral oophorectomy, or hyperprolactinaemia.	Introital pain and with penile-vaginal movement. Possible postcoital burning. Deeper dyspareunia when vaginal atrophy advanced.	Pallor, dryness, increased fragility and thinning of vulvovaginal epithelium, vaginal shortening, loss of rugae, narrowing, or urethral caruncle.	Local ET is highly recommended.[a] Low-dose estradiol by vaginal ring or tablet can be equally effective, but serum levels remain postmenopausal.[b] Tibolone improves this disorder beyond placebo.[c] Frequent sexual arousal and (if necessary) non-penetrative activity could promote genital health.[d] Give dopaminergic drugs such as bromocriptine, cabergoline, or both to reduce prolactin; with surgery or radiation as appropriate.
Chronic (abdominal) pain; Endometriosis; Chronic PID; IBS; Crohn disease; Ulcerative colitis; Ovarian tumour; Abdominal wall pain.	Deep dyspareunia. IBS also associated with introital pain from comorbid VVS.	General tenderness to deep bimanual examination.	Sexual dysfunction is highly prevalent in such patients.[e] Women report deep dyspareunia. Organic disorders should be treated accordingly but sexual dysfunction may still need to be specifically managed. Irrespective of the organic or functional nature of the pain, a history of possible negative sexual experiences should be elicited before any procedures or treatment.[f]
Lower urinary tract symptoms (LUTS) with urinary incontinence.	Introital and deep dyspareunia or vulvar burning after sexual intercourse.	Perineal and vulvar inflammation.	Voiding dysfunction, recurrent bacterial cystitis, hypoactive sexual desire, and sexual pain disorders are highly correlated.[g] For recurrent cystitis give local ET,[b] antibiotic self-treatment or prevention, and postcoital micturition (based on CE). In case of prolapse, surgical treatment can be curative but can also have undesired effects on sexual functioning.[i]
Pelvic radiation.	Introital and deep dyspareunia.	Thinning and fragility of vaginal epithelium, loss of elasticity, stenosis, or foreshortening.	Preventive measures, such as transposition of the ovaries to prevent ovarian failure. Therapeutic options based on CE include couple counselling about non-penetrative sex, topical estrogen, lubricants, vaginal inserts, and vaginal reconstruction.
Chronic vulvovaginal candidiasis associated with diabetes and HIV.	Introital dyspareunia and with penile-vaginal movement.	Erythema, swelling of vulva, and thick clumpy white or pale yellow vaginal discharge.	Oral agents recommended for recurrent symptomatic candidiasis.[j]
Vulvar vestibulitis syndrome (VVS) associated with IBS, fibromyalgia, interstitial cystitis (IC), and other pain syndromes.	Superficial vulvovaginal pain on (attempted) penetration, pain on non-penetrative vulvovaginal touching, postcoital burning, or burning from partner's ejaculation fluid.	Variable erythema of the vestibule. Allodynia typically located between 4 and 8 o'clock on the introitus, just exterior to the hymenal ring but can involve the skin around the openings of the Skene's ducts or the whole introital rim. Hypertonic pelvic floor muscles. Pain with attempted digital or speculum entry.	Vaginal muscle EMG biofeedback with pelvic floor physical therapy and CBT have been shown to have clinical benefit, but evidence is limited.[k] Based only on CE is treatment with topical estrogen, cromolyn, Xylocaine, capsaicin, or botulinum toxoid injections. Based on CE, and the not yet proven assumption that neuropathic pain is at least in part responsible for the pain of VVS, give TCAs or AEDs. For comorbid IC, DBPCTs have shown benefit of oral or intravesical pentosan polysulfate, intravesical dimethyl sulfoxide or resiniferatoxin (vallinoid). Based on CE, there may also be benefit from antihistamines, quercetin, intravesical heparin, lidocaine, or a combination.[l] Excision of the affected regions (vestibulectomy, vestibuloplasty, or perineoplasty) can reduce pain in the short term but long-term sexual outcome less clear.[m]
Dysaesthetic vulvodynia.	Introital dyspareunia, and with penile-vaginal movement.	None.	Vulvar burning and pain that causes sexual and psychological distress accompanied by the complete absence of any physical abnormality on examination, in biopsies or culture. Based on CE, TCAs or AEDs can be partial benefit.
Genital mutilation.	Introital pan and with penile-vaginal movement and deep dyspareunia.	Type I: all or part of the clitoris and its prepuce or skin excised. Type II: clitoris excised, labia minora partly or totally removed. Type III: all external genitalia excised, vaginal opening closed except for a matchtip-sized hole to allow urine and blood to escape.	Experienced by an estimated 130 million women, in particular from North Africa, the Middle East, and Southeast Asia. Based on CE, use a respectful approach and provide information about health consequences. Offer sexual counseling, psychotherapy, and support groups. Offer to repair the vulva, vagina, or both. Involve the partner, the family, or both in decisions. Clarify the legal and ethical responsibility of the physician, who must decline any request to restitch after childbirth. Offer specific management of sexual dysfunction as needed.[n]

(continues)

TABLE 9.10 Subtypes of Chronic Dyspareunia in Women *(Continued)*

Medical Disorder	Type of Dyspareunia	Findings on Physical Examination	Therapeutic Options and General Comments
Dermatological diseases.	Can be introital dyspareunia (eg, eczema) or deep (eg, lichen planus affecting vagina).	Benign non-STD can be atopic eczema, contact dermatitis (including iatrogenic), lichen simplex, lichen sclerosus, lichen planus, psoriasis, hidradenoma, foxfordyce, chronic vestibular gland infection, pediculosis pubis, pin worm infections, Behçet's aphthous ulcers, cicatricial pemphigoid, pyoderma gangrenosum, anorectal Crohn burn, or trauma. STD can be HSV, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, condylomata acuminata, or molluscum contagiosum. Neoplasia can be VIN, vulvar Paget's, or melanoma.	For a benign non-STD, based on CE,[a] give corticosteroids (oral, topical, or injectable); immunosuppressive drugs (azathioprine, dapsone, tacrolimus, pimecrolimus, thalidomide, or infliximab); immune augmentation drugs (imiquimod); surgery; behavioral and physical therapy; and biofeedback. Also offer psychosexual support for sexual problems resulting from limited skin contact, visible symptoms, disrupted self-image, inability to meet a partner, shame, lack of confidence, or a combination of these. For treatment options for STD consult Guidelines from ISTI, WHO and CDC USA.[p,q] Asymptomatic shedding and further infection necessitate strong encouragement of protective measures and safe sex. For neoplasia attempt surgery, laser therapy with radiation, or chemotherapy, as appropriate. Sexual activities do not stop for most couples. Based on CE, psychosexual counseling can be of benefit, in particular in the first year after treatment.[r]
Anatomical variations.	Introital or deep dyspareunia depending on abnormality.	Labial fusions, rigid hymen, vaginal septum, vaginal agenesis, or hypoplastic vagina.	Based on CE, in case of vaginal agenesis non-surgical options can be highly successful.[s] Surgical intervention is recommended for persistent hymen, labial fusions or a painful vaginal septum.

PID, pelvic inflammatory disease; IBS, irritable bowel syndrome; CE, clinical experience or open label studies; EMG, electromyography; CBT, cognitive behavioral therapy; TCA, tricyclic antidepressant; AEDs, antiepileptic drugs; DBPCTs, double-blind placebo-controlled trials; STD, sexually transmitted disease; HSV, herpes simplex virus; ISTI, International Society for Infectious Diseases; VIN, vulvar intraepithelial neoplasia; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention.

[a] North American Menopause Society. Amended report from the NAMS Advisory Panel on Postmenopausal Hormone Therapy. *Menopause*. 2003;10:6–12.
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[e] Verit FF, Verit A, Yeni E. The prevalence of sexual dysfunction and associated risk factors in women with chronic pelvic pain: a cross-sectional study. *Arch Gynecol Obstet*. 2006;274:297–302.
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[h] Eriksen BC. A randomized, open, parallel group study of preventive effect of an estradiol-releasing ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol*. 1999;180:1072–1079.
[i] Rogers GR, Villarreal A, Kammerer-Doak D, et al. Sexual function in women with and without urinary incontinence and/or pelvic organ prolapse. *Int Urogynecol J Pelvic Floor Dysfunct*. 2001;12:361–365.
[j] Goswami D, Goswami R, Vanerjee U, et al. Pattern of Candida species isolated from patients with diabetes mellitus and vulvovaginal candidiasis and their response to single dose oral fluconazole therapy. *J Infect*. 2006;52:111–117.
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[m] Van de Werf-Eldering MJ, Batstra L. To cut or not to cut: treatment of vulvar vestibulitis syndrome. *J Psychosom Obstet Gynaecol*. 2004;25:77–79.
[n] Basson R, Weijmar Schultz WCM, Binik YM, et al. Women's sexual desire and arousal disorders and sexual pain. In: Lue TF, Basson R, Rosen R, et al, eds. *Sexual Medicine: Sexual Dysfunctions in Men and Women*. Paris: Health Publications; 2004:922–925.
[o] Foster DC. Vulvar disease. *Obstet Gynecol*. 2002;100:145–163.
[p] World Health Organization. European STD guidelines 2001. *Int J STD AIDS*. 2001;12:1–107.
[q] Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep*. 2006;55:1–94.
[r] Weijmar Schultz WCM, Van de Wiel HBM. Vulvar vestibulitis syndrome: care made to measure. *J Psychosom Obstet Gynaecol*. 2002;23:5–6.
[s] Nadarajah S, Quek J, Rose GL, et al. Sexual function in women treated with dilators for vaginal agenesis. *J Pediatr Adolesc Gynecol*. 2005;18:39–42.
From Basson R, Schultz WW. Sexual sequelae of general medical disorders. *Lancet*. 2007;369:409–424.

can be difficult patients to work with because of their sense of hopelessness and helplessness about their condition. It may be extremely difficult to do a pelvic exam in patients with vaginismus or dyspareunia. If they have an intimate partner, their relationship may be strained because sexual interactions are so challenging for women with vulvar pain. Remission without treatment is atypical. Misdiagnosis is common because these disorders are infrequently and inadequately covered in physician's training programs.

When evaluating the pelvic pain patient, be sure to take a thorough history and perform a thorough pelvic exam. For the major components of history and physical exam in women with dyspareunia, see Table 9.11.

Treatment for the sexual pain disorders varies significantly from the treatment of chronic pelvic pain (CPP), which is discussed in greater detail in Chapter 7. The best approach is a multidisciplinary one that involves a gynecologist, a mental health professional with training in sexuality, a pelvic floor physical therapist, and, many times, a dermatologist in the comprehensive initial assessment. A pelvic floor physical therapist can be located at www.apta.org (the American Physical Therapy Association). In addition, a sex therapist can address intrapersonal as

TABLE 9.11 Evaluation of the Pelvic Pain Patient

History

1. Develop a timeline of the dyspareunia:
   a. Has intercourse always been painful?
   b. Has tampon use always been painful?
   c. Did the pain start acutely or gradually?
   d. Is the pain only during intercourse or is there pain without provocation?
   e. Since the pain began, have there been episodes of completely painfree sex?
2. Determine the location of the pain:
   a. Is the pain upon insertion?
   b. Is the pain inside the vagina?
   c. Is there pain with deep thrusting?
   d. Are there any positions that are more/less painful?
   e. Is there pain with clitoral stimulation?
   f. Is there post-coital pain?
3. Elicit symptoms:
   a. Is there burning, rawness, cutting, searing, aching, sharp, full, throbbing, tearing, sandpaper, dry, itchy sensations?
   b. Is there dysuria, hesitancy, urgency, frequency, incomplete emptying of the bladder?
   c. Is there constipation?
4. Cover additional important questions such as:
   a. History of oral contraceptive use
   b. Past treatment for recurrent infections? History of sexually transmitted infections?
   c. Use of antifungal creams in the past? Did they burn?
   d. History of vulvar biopsy?
   e. Nature of pain, ie, is the pain worse/same/better with condom use?
   f. Bleeding during/after sex?
   g. Lacerations or fissures during or after sex?
   h. History of oral lesions?
   i. History of sensitive skin?
   j. History of allergies to topical medications?

Physical exam

1. Careful visual inspection of the vulva
2. Vulvoscopy
3. Q-tip test
4. Vaginal examination – insert a pediatric speculum into the vagina without touching the vestibule
5. Manual exam: insert one finger through the hymen without touching the vestibule. Is there mucosal tenderness?
6. Pelvic floor musculature examination
7. Palpate the urethra and bladder – is there intrinsic tenderness?

From Goldstein A. A multidisciplinary approach to female sexual pain disorders for the advanced clinician. Presented at: Annual meeting of the International Society for the Study of Women's Sexual Health; February 2010; St. Petersburg, FL.

TABLE 9.12 Main Components of Treatment of Dyspareunia

1. Encourage/normalize nonpenetrative sex.
2. Medically address any specific pathology (e.g., recurrent tears of the posterior fourchette, vulvovaginal atrophy, lichen sclerosus, endometriosis, allodynia of VVS).
3. Consider physical methods: pelvic muscle physiotherapy positive/negative biofeedback to change pelvic muscle hypertonicity.
4. Address any associated anxiety, catastrophizing, self-blame, guilt, anger.
5. Address fertility issues, and arrange home or clinic insemination of partner's semen.

VVS, vulvar vestibulitis syndrome.
From Gibbs RS, Karlan BY, Haney AF, et al. *Danforth's Obstetrics and Gynecology*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

well as relationship issues. A sex therapist can be found at www.aasect.org (the American Association of Sex Educators, Counselors, and Therapists).

Treatment for dyspareunia is multimodal, and attention should be focused on six areas: the mucous membrane, the pelvic floor, the experience of pain, sexual and relationship function, psychosocial adjustment, and genital mutilation/sexual abuse (Table 9.12). Treatment for vaginismus has focused primarily on the vaginal muscle spasm and typically involves cognitive behavioral therapy as well as vaginal dilators and relaxation techniques.[81] The misconception is that vaginismus is an easily resolvable condition, and although treatment "success" may allow for vaginal penetration for intercourse, it may not include success in addressing the patients' subjective experience of pain, fear, and other issues of sexual function. Yet studies indicate that fear is an important factor in vaginismus and must be addressed in treatment.[112]

Treatment of sexual pain may include the use of topical creams; lubricants; oral medications; dilator therapy; specific pain management techniques such as nerve blocks, acupuncture, and hypnosis; surgery; and numerous complimentary or alternative therapies including diet and herbal remedies.[113] If dilator therapy is used, the goal is desensitization, not to simply enlarge the vaginal orifice. Instructions for the use of vaginal dilators (such as those from, e.g., Soul Source [www.soulsourceenterprises.com]) include the use of liberal amounts of water-soluble lubricant, a progression to the next larger size only when the patient is comfortable with the current size, and insertion of the dilators in private in order to minimize self-consciousness and maximize the sense of control.

Although they have not been extensively studied, pelvic floor electromyography (EMG) biofeedback and physical therapy, Kegel, reverse Kegel and relaxation exercises, transcutaneous electrical nerve stimulation (TENS), and (group) cognitive behavioral therapy are clinically useful interventions with long-term benefit.[114] Treatment often requires the collaboration of a pelvic floor physical therapist to address chronic pelvic floor hypertonicity. Psychotherapists may provide assessment and treatment of coexisting depressive and anxiety symptoms, offer behavioral treatment for coping with pain conditions, and assist the patient in expanding her sexual repertoire.

There is a small but growing movement within the field of female sexual health proposing that dyspareunia and vaginismus should be classified as pain disorders rather than sexual pain disorders.[115] In the past, the assessment of pain during intercourse focused on the sexual aspects, with an underlying assumption that improving the woman's technique, or her partner's, will improve her pain. For women, it is not that the pain is sexual but rather, the sex is painful. There is no significant evidence that improving the woman's sex life resolves dyspareunia for most women. Hence, the need is

for a modification in our understanding of these problems. The diagnostic shift being proposed refocuses the primary treatment problem as the anticipated experience of genital pain and/or vaginal penetration, and that sexual complaints are secondary to these issues. Thus, the clinical focus would shift from sex to the experience of pain and fear.

SEX, SEXUALITY, AND SPECIFIC LIFE CONTEXTS FOR WOMEN

Pregnancy

Pregnancy is one of the more profound experiences of a woman's life. It represents an extraordinary time of change for a woman, physically, emotionally, sexually, spiritually, and interpersonally. The changes pregnancy brings are sweeping and may include changes in a couple's relationship, coping with issues of planned versus unplanned and desired versus undesired pregnancy, anxiety around developing a parental relation or strengthening an existing one, past experiences with pregnancy, along with the physical and hormonal changes that can create a negative self-image, mood lability, difficulty and discomfort in performing vaginal sex, modifications on neurotransmitters' concentrations, etc. will all interact and strongly influence the sexual life of the couple in pregnancy. Pre-existing sexual dysfunctions can worsen during pregnancy.[116] Even for women without a history of sexual dysfunction, many report a decrease in sexual desire during the pregnancy as well as a decreased frequency of intercourse and a decrease in sexual satisfaction as her gestation advances. Compared to prepregnancy, the length of intercourse as well as the ability to experience orgasm are decreased in the later stage of pregnancy.[117] The clinician should remember that both women and their partners often have concerns about possible complications in the pregnancy that may result from sexual intercourse (e.g., preterm labor, miscarriage, or harm to the fetus), and these need to be directly asked about and addressed.[118] It is important to reassure couples that in a healthy pregnancy, sex may continue throughout.

In many studies, there seems to be a steady decline in the frequency of sexual intercourse during pregnancy that may continue for up to 3 to 6 months postpartum. After this, there seems to be a gradual and steady recovery.[119–121] Research suggests that the changes in sexual activity during the first and second trimesters may be small, and it is in the third trimester that the largest decline in sexual activity is seen.[122,123] One study reported that between 22 and 50% of women found sex painful late in their pregnancy.[114] This is also a time when a woman may become more self-conscious about weight gain and body image, which can impact her interest in sex.

Sexual issues do not end after a woman gives birth. In fact, many women describe changes in their sexual experience that last up to a year after childbirth.[124] One study found that up to 84% of couples reported sexual issues at 4 months postpartum.[125] Perineal pain after obstetrical lacerations or an episiotomy may persist after the postpartum period for some women.[126–128] Some studies suggest that 7 to 10% of women have dyspareunia a year postpartum.[129] Potential causes of this dyspareunia include anatomic changes or distortion, persistent granulation tissue, and the development of a trigger point. If the patient had myofascial pelvic pain syndrome prior to the pregnancy, it may be worsened after delivery. Treatment for these patients depends on the etiology and must be individualized.

Women who are breast-feeding may contend with vaginal dryness and atrophic genital changes due to lowered levels of estrogen. The prolactin increase while breast-feeding may result in lowered sexual desire. Some women are embarrassed by leaking breast milk while making love. Lack of rest makes all of these issues more difficult to cope with and further diminishes her sex drive. Unfortunately, about one-third of women develop sexual issues as a result of pregnancy that remain as long-term sexual problems.[130] However, one study found a positive correlation between a woman's sexual function and number of offspring.[116]

The clinician should elicit any sexual health concerns women and their partners may have during and after pregnancy and fully evaluate them. It is important that couples are told that a decline in libido, desire and orgasm, along with a decrease in sexual frequency during pregnancy and in the early months postpartum does not represent a pathologic condition per se. Couples should be encouraged to find creative ways to maintain intimacy: Sexual intimacy does not require intercourse. Encourage the mother to find time for herself so that she is not feeling pulled from her child to her husband without a break. Otherwise, she will experience her husband as just another demand on her time and attention, and this will decrease her interest in intimacy. Encourage the couple to keep touching, hugging, and kissing to maintain nonsexual physical contact.

Menopause and Beyond

Clinicians are seeing a large and growing number of sexually related complaints among menopausal women, in part because of the changing demographics in most industrialized countries. The average life expectancy in the United States and other developed nations is older than 80 years of age; as a result, many women will live for 40 years or more in the menopausal stage of life. Studies show that women and men in their 60s, 70s, and 80s in the United States continue to be sexually active.[131,132] Most women expect that they will want and

enjoy sex less with age. However, research suggests that there is actually much variability among women's experience of sexuality in later life, and some women report enjoying sex even more as they age. For older women, having a partner, good health, and current estrogen use are all positively associated with sexual activity.[133–135] A recent study reported that the most common sexual problem in older women is lack of sexual interest.[136,137] In one study of men and women all older than 70 years of age, 41% of the male participants and 18% of the female participants reported engaging in some type of sexual activity, and the most commonly cited reason for being sexually inactive among women was "no desire," whereas most men reported "erectile dysfunction" as the reason for not engaging in sexual activities.[138]

When discussing sexual issues with a mature woman, keep in mind that her sexual experience is unique to her, and there is no single common paradigm for sexuality in later life. Because women older than 65 years are four times as likely as men to be widowed, more and more women spend their later years without an intimate companion. However, do not assume that an unpartnered woman is asexual. Women who wish to do so can maintain a sexual connection with their bodies via masturbation. Older women may actively be seeking a partner or are open to the idea of a sexual encounter, so issues around the prevention of sexually transmitted infections need to be addressed.

Common age-related sexual concerns include low sex drive, vaginal atrophy, vaginal dryness, dyspareunia, and decreased ability to orgasm/anorgasmia. Dyspareunia has a number of causes, but lack of estrogenization is a common cause in women experiencing estrogen deficiency due to any etiology at any age. With menopause, and in the years thereafter, there may be ongoing involution at the introitus, even though the upper two-thirds of the vagina may continue to be spacious. ET, used topically, may help to prevent or diminish the involution that occurs. In some instances, if the involution is severe, dilator therapy in conjunction with a topical estrogen cream may be indicated. (For more discussion on the use of estrogen or other hormone therapies in menopausal women, see Chapter 24.)

In spite of the fact that sex is generally less satisfying over time,[139] distress about sexual dysfunctions tends to decrease in older women as compared to their younger counterparts.[140] Nonetheless, prevalence studies indicate that the majority of older women remain at least moderately emotionally sexually satisfied.[141] It is important to note that some research suggests that the quality of a woman's relationship is a more primary factor in her sexual satisfaction than age-related physical changes.[142] It is also likely that woman's sexual responsiveness changes with age, such that older women rely more on loving cues from their partner, whereas younger women may depend more heavily on physical sensations for sexual pleasure.[143] As a result, mature couples may well benefit sexually from attention to the quality of their intimate relationship.

Sexual Abuse History

Prevalence rates indicate that approximately 33% of girls younger than age 18 years have been victims of sexual abuse.[144] This astounding number includes any unwanted sexual interaction ranging from intercourse to kissing. Sexual abuse can negatively impact a woman's sexual experience well into the future, and sexual dysfunctions are common among sexual abuse survivors.[145] The three factors that most affect adult sexual desire and function after sexual trauma are the type of sexual trauma; how the trauma(s) were dealt with at the time they occurred; and, most importantly, whether the person views himself or herself as a survivor or victim.

Past sexual abuse or trauma may result in women fearing emotional and/or physical intimacy, or fearing loss of control during sex. An abuse survivor may experience flashbacks, dissociative episodes, feelings of shame and guilt, compulsive sexual behavior, and sexual aversion.[146] As a result, a woman's partner often becomes confused and overwhelmed with whether or not to pursue a sexual relationship with her.

There is some evidence that sexual and physical abuse might be related to increased pain intensity, functional impairments, and psychological distress in different populations of pain patients, including women with CPP.[147,148] In treating patients with sexual dysfunction, and a history of past sexual abuse or trauma, it is imperative that a multidisciplinary approach be taken and include the services of a mental health professional skilled in issues of sexuality.

The Unconsummated Marriage

Although reliable prevalence rates have yet to be determined, unconsummated marriages (UM) are probably more common than is suspected in traditional societies. The little research that is available suggests that this is actually a diverse group of people representing a multifactorial etiology. There is also much variability in the amount of distress experienced as a result of not consummating the marriage, and couples who enjoy a satisfying emotional and/or physically intimate relationship without intercourse are generally less distressed.[149] UM should be differentiated from the established individual causes of vaginismus, dyspareunia, phobias, or male sexual dysfunctions (ED or ultrapremature ejaculation). Establishing the frequency of UM is difficult because it can last over variable time spans and also because many couples avoid consultation. In an update that ranged from 1990 through 2000 and covered 11,000 cases surveyed in one institution, 2% of consultations were for UM.[150]

Most commonly, vaginismus and phobia to penetration in females and phobias and impotence in males underlie the UM cases.[150] But it is not simply that there is a concurrence of a female sexual dysfunction and a male sexual dysfunction in the same couple. In the majority of cases, the principal element for diagnosis and therapy lies in the couple's relationship dynamics. The underlying cause in UM is sexual anxiety, which shows up as coital phobias, vaginismus, dyspareunia, ED, and ultrapremature ejaculation; because the anxiety encloses both members of the couple, it should be treated and solved accordingly.

Because these emotional and interpersonal issues are often complicated and time consuming to address, a referral to a qualified therapist is probably warranted.

The Sexless Marriage

It has been estimated by one author that an astounding 20% of marriages are sexless.[151] A sexless marriage is defined as having sex six or less times in a year. Some couples are comfortable with this arrangement because sex is not important to either partner. However, more often than not, one or both partners in a sexless marriage finds the lack of intimacy to be extremely uncomfortable emotionally and/or physically. Sexual dysfunction is common in a sexless marriage—low desire, ED, sexual pain, and arousal disorder are frequent concerns. Oftentimes, the couple remains secretive about these issues because they feel embarrassed or ashamed. Simply informing your patient that sexless marriages are relatively common can go a long way in alleviating this discomfort.

Treatment of a sexless marriage typically requires the help of a sex therapist because it is very difficult for a couple to resume a satisfying sexual relationship once they have been sexually stagnant for an extended period of time.

SEXUAL ISSUES FOR WOMEN WITH CHRONIC ILLNESS

Advances in surgical and medical treatments of illness have led to longer lives for patients with chronic illness and, in turn, an increasing emphasis on their quality of life, including their sexual life. Even with chronic illness, past or present cancer, sexuality remains extremely important for both men and women. Assessment and management of sexual dysfunction is a core component of optimizing their health and quality of life. Unfortunately, women with chronic illnesses often struggle with sexual issues, and these issues are frequently overlooked[152] (Table 9.13). Between their medical issues, the side effects of their medications, accompanying mood issues such as depression and/or anxiety, and fatigue, multiple sexual difficulties are common (Table 9.14). Commonly, women with chronic illness are older and have postmenopausal issues as well, such as dryness and pain with intercourse. In addition, many have pre-existing sexual concerns which are made increasingly complex by their chronic illness. Some of the more common chronic illnesses that negatively impact sexuality include

TABLE 9.13 Overview of Medical and Psychological Effects of Disease on Sexual Function

Medical factors resulting from disease, treatment, or both

- Fatigue, pain, incontinence, or changed anatomy of sexual organs
- Reduced mobility which limits ability to caress, stimulate self or partner, or engage in intercourse
- Changed physical sensations, such as itching, irritation, or hypersensitivity
- Interruption of sexual response, infertility, dyspareunia, or painful ejaculation or orgasm
- Angina or dyspnea from sexual stimulation

Psychological response to illness or sexual dysfunction

- Fear that sex could be dangerous, and provoke myocardial infarction or cerebral vascular accident
- Fear of infection or conviction that illness was caused by sexual activity (eg, cancer as punishment)
- Preoccupation with illness or loss of control and independence
- Disrupted sexual self-image or feeling failure as a sexual partner or potential parent
- Anxiety, depression, anger, shame, guilt, stress, or emotional liability
- Avoidance behavior, fearing pain or rejection due to disfigurement or stomas
- Repeatedly remembering traumatic medical procedures to sexual parts

Personal psychological factors

- Limited coping mechanisms or negative attitude
- History of limited or unrewarding sexual experiences
- Past abuse (sexual, physical, or emotional)

Relationship and social factors

- Lack of intimacy, trust, or freedom from abuse
- Difficulties with communication, power regulation, or role changes
- Partner's negative reactions to illness
- Partner's sexual dysfunction
- Inability to meet a partner or lack of information about sexual rehabilitation
- Social obstruction by third parties (eg, at a hospital or nursing home)
- Cultural non-acceptance of sexuality when ill or old

From Basson R, Schultz WW. Sexual sequelae of general medical disorders. *Lancet*. 2007;369:409–424.

TABLE 9.14 Drugs Associated With Sexual Dysfunction

Anorectics	Diuretics
Antiandrogens	Hormones
Antiarrhythmics	Lipid-lowering agents
Anticholinergics	Neuroleptics
Antihistamines*	Oncologic agents
Antihypertensives	Opiates
Antivirals	Psychotropics
Anxiolytics	Recreational or illicit drugs
Corticosteroids	Sedative-hypnotics
Decongestants	Stimulants

*Including histamine H_2 blockers.

From Nusbaum MRH. *Sexual Health*. Leawood, KS: American Academy of Family Physicians; 2001. Home Study self-Assessment Program; with data from Differential diagnosis of sexual dysfunction. In: Crenshaw TL, Goldberg JP, eds. *Sexual Pharmacology: Drugs That Affect Sexual Functioning*. New York: Norton; 1996:15–21; Roberts LW, Fromm LM, Bartlik BD. Sexuality of women through the life phases. In: Wallis LA, Kasper AS, eds. *Textbook of Women's Health*. Philadelphia: Lippincott-Raven; 1998:763–80.

arthritis, diabetes, cardiac disease, neurologic disease, and cancer.[1,153]

Chronic illness, surgery, or other treatment modalities for chronic disease, including cancer, may be associated with neurologic, vascular, endocrinologic, musculoskeletal, or psychological changes that interfere with normal sexual function. There are few, if any, chronic conditions that require a restriction of sexual activity, although couples may need to change their sexual activities to accommodate physiologic or mechanical limitations imposed by the illness or sequelae of treatment(s). Chronic medical illnesses tend to disrupt the desire and arousal phases of the sexual response cycle. Treatments for chronic illnesses may disrupt the normal sexual response cycle. For example, antihypertensive drugs may negatively affect arousal, and psychotropic agents may interfere with desire, arousal, and disrupt orgasm. Surgical therapies or radiation may interfere with arousal and orgasm by disrupting delicate sympathetic and parasympathetic pathways.

A full discussion regarding the impact of specific illnesses and their potential effects on sexuality and treatment options is beyond the scope of this chapter. See Table 9.15 for things to consider when doing an assessment of sexual dysfunction associated with chronic illness. For an overview of general strategies for optimizing sexual functioning, see Table 9.16.

Working with these patients can be frustrating because of their complexity; nonetheless, sexuality and intimacy are basic human needs, and people who are ill still desire closeness with those they love.[154] Couples need to be reassured that sexual intimacy may continue to be part of their relationship, and treatment options and approaches for sexual complaints may be available. Most patients and their partners want to talk with their care providers about the impact of illness on their sexuality.

TABLE 9.15 Assessment of Sexual Dysfunction Associated With Chronic Illness

- Review past medical and psychiatric history
- Review current medical status: consider respiratory, cardiac, mobility, and continence requirements for sexual activity including intercourse, self-stimulation, and orgasm
- Review current medications
- List the sexual dysfunctions, their duration, and whether the dysfunction is also present with self-stimulation or with other partners
- Clarify relationship status and quality
- Review the environment for sex: home/institution/"medicalization," e.g., hemodialysis machines, respirators, lack of independence in daily living
- Review any chronic pain
- Assess consequences of illness on sexual self-image (concerns with regard to attractiveness, physical appearance)
- Review dysfunctions in detail:
  - Clarify motivations for sex including "desire/drive" and desire to satisfy partner; identify reasons for avoiding sex
  - For ED check erections on waking from sleep
  - Clarify subjective arousal/excitement, pleasure
  - Review variety and usefulness of sexual stimuli
  - Assess couple's sexual communication
  - Consider the importance of distracting thoughts or negative emotions during sex
  - Determine if wanted orgasms are possible, very delayed, nonintense, painful
  - Identify ejaculation difficulties—delayed, too early, painful, absent
  - Review if intercourse is possible
  - Assess female dyspareunia: introital, deeper, how constant, exacerbation from partner's ejaculation fluid, postcoital burning, postcoital dysuria
  - Assess male dyspareunia; immediate, delayed, any physical changes
- Clarify sexual response pre illness: any dysfunction, how rewarding, how important was sex, any desire discrepancy, paraphilia
- Review impact of medications on desire and response
- Review treatment of sexual dysfunction to date
- Complete a full physical exam including genital exam: usually necessary because of the medical condition, particularly important for neurological illness and when there is ED, dyspareunia, or pain with arousal
- Complete psychological exam exploring mood, anxiety, insomnia, and life stressors
- Laboratory investigations—as necessary especially when needed to monitor anemia, high prolactin, hypogonadism, thyroid disorders. Estrogen levels usually assessed by the history and the genital/pelvic examination
- Specialized testing of genital blood flow, e.g., Doppler studies of cavernosal flow for ED—rarely indicated as results do not alter treatment options

ED = erectile dysfunction.
From Basson R, Rees P, Wang R, et al. Sexual function in chronic illness. *J Sex Med.* 2010;7:374–388.

TABLE 9.16 General Strategies for Optimizing Sexual Functioning in Patients With Chronic Illness

Dietary strategies

Avoiding tobacco in any form
Limiting alcohol intake
Delaying sexual activity until 2 or more hours after drinking alcohol or eating

Medication strategies

Taking pain medications (if needed) about 30 minutes before sexual activity
Reducing or stopping medications that have a negative impact on sexual functioning (see Table 9.14)
Treating depression

Environmental strategies

Planning sexual activity for time when energy level is highest (and when rested and relaxed)
Planning sexual activity for time of day when symptoms tend to be least bothersome
Avoiding extremes of temperature
Experimenting with different sexual positions or using pillows to maximize comfort
Maintaining physical conditioning to highest possible level

Psychologic strategies*

Enhancing sexual expression though use of senses
Maximizing use of nonsexual intimate touching
Communicating likes, dislikes, and needs to partner
Using self-stimulation as needed to reduce anxiety, help with sleep, and provide general pleasure
Using self-help books that cover the subject of chronic illness and sexual activity

*The patient's sexual partner may need to accept the patient's lack of sexual interest or decision to have no sexual partner.
From Nusbaum MRH. *Sexual Health*. Leawood, KS: American Academy of Family Physicians; 2001. Home Study Self-Assessment Program.

Breast Cancer and Sexuality

Breast cancer is the most common cancer diagnosis among women. Due to modern medical advances, more and more women are surviving breast cancer and seeking to improve their quality of life. Cancer treatment can have a profound impact on a woman's sexual experience. For women with past or present breast cancer, there are many potential contributors to changes in their sexual health: alterations in body image that may diminish feelings of sexual desire, changes in sexual self-esteem and self-efficacy, vulvovaginal atrophy secondary to chemotherapy, and/or adjuvant hormone therapy that may lead to dyspareunia and later, decreased desire. The use of long-term medications such as aromatase inhibitors or antiestrogens may further contribute to vulvar and vaginal atrophic changes with their potential attendant changes in sexual health and satisfaction. Even the systemic side effects from cancer therapies such as hair loss, fatigue, nausea, dry mouth, cramps/bloating/diarrhea, body and joint pain/stiffness, and peripheral neuropathy impact a woman's sexual experience.[155]

Because breast cancer is often hormonally sensitive to estrogen and/or progesterone, the treatment of vulvovaginal atrophy with hormonal agents is highly controversial. There is increasing interest in the use of localized therapy with vaginal estrogen preparations such as low-dose vaginal 17 beta-estradiol tablets (10 mcg) or the vaginal estradiol ring because of their minimal systemic absorption and efficacy in the treatment of vaginal dryness and pain.[156] The long-term safety of such therapy remains unknown. In some studies, bupropion increased sexual desire and frequency of activity in noncancer patients with antidepressant-induced sexual dysfunction, but its use has not been studied in women with a concurrent diagnosis of breast cancer.[157]

Over-the-counter moisturizers and lubricants, as well as maintenance of sexual activity, are useful in managing vaginal dryness and dyspareunia.[158] Intravaginal moisturizers (i.e., Replens [polycarbophil]; Lil' Drug Store Products, Cedar Rapids, IA, USA; Liquibeads [silicone-based capsules]; McNeil, Fort Washington, PA, USA) used two to three times weekly may be helpful in maintaining vaginal moisture and pH balance. There are many types of over-the-counter lubricants: water-based, petroleum-based, natural oils, and silicone. Water-based lubricants are generally compatible with latex condoms, do not stain, and rarely cause irritation but dry out with extended activity. Water-based lubricants with minimal additives such as Good Clean Love: Almost Naked (Eugene, OR, USA), Astroglide (Biofilm, Vista, CA, USA), or Slippery Stuff (WalMed, Puyallup, WA, USA) are available. Petroleum-based products such as petroleum jelly (Vaseline, Unilever; London, UK) should not be used with latex condoms, diaphragms, or cervical caps and may be irritating to the sensitive vagina and vulva. Natural oils (avocado, olive, peanut, or corn) are safe, nonstaining, and nonirritating to vagina. Silicone lubricants (KY Intrigue, McNeil, Fort Washington, PA, USA) are nonirritating, long lasting, and waterproof.

There are a variety of nutraceutical products on the market, for example, a botanical feminine arousal oil, Zestra (Semprae Laboratories, Saddle Brook, NJ, USA) that purportedly augments the genital arousal response. In many instances, clinical safety and efficacy data on these products are lacking and patients should be advised to carefully read ingredients of "natural" and herbal products prior to their use. Commercially available vibrators/self-stimulators can also be helpful for women who benefit from extra stimulation to erotic areas of the vagina and clitoris.

A multimodal approach is usually the best in helping couples cope with the sexual and relationship challenges after breast cancer.[159] In one review, researchers found that interventions that focused on the couple rather than on the individual woman had the most likelihood of yielding both statistical and clinical improvements.[160]

Sexual dysfunction is a complex disorder, and when it occurs in the context of past or current cancer, it may only magnify an already significant stressful life event. A multimodal approach to therapy, including attention to both the individual woman and the couple, should help to ameliorate or alleviate some of the stress.

MALE/PARTNER SEXUAL DYSFUNCTION

Male sexual dysfunction is a very real problem for men of all ages. The most common sexual dysfunctions for men include rapid ejaculation (21%), low sexual desire (5%), and ED (5%).[1] However, gynecologic folklore still references the 50/60/70 rule, suggesting that 50% of men older than age 50 years have ED, 60% older than age 60 years, and 70% older than age 70 years have some degree of ED. In addition, low libido is being increasingly diagnosed in men, probably in part due to life stress, side effects of common medications, and the cultural tendency to focus on mental activity and thinking at the expense of body rhythms and instinctual drives. Research consistently demonstrates that sexual dysfunction in a woman's intimate partner significantly impacts her satisfaction and enjoyment of sex.[161] For example, some research suggests that many women require 15 minutes or longer of active penile–vaginal intercourse to achieve orgasm.[162] If her partner ejaculates quickly, or has ED, she may not find sex as pleasurable. Women can lose interest in sex and present with low libido in such situations. When men struggle with low desire, women may feel emotionally or physically undesirable or ignored.

In one study based on a sampling of men and women aged 57 to 85 years, the analysis demonstrated a significant association between feeling bothered by partner's sexual problems and depressive symptoms. Interestingly enough, however, for women, the level of perceived supportiveness of their partner helped to compensate the degree to which they were bothered by their partner's

sexual unresponsiveness, particularly with regard to depressive symptoms. This was not found in men.[163]

ED contributes to sexual and emotional distress felt by the couple and increases the likelihood that both partners will experience sexual dysfunction themselves.[164–166] One of the primary reasons men with ED seek successful treatment is their concern for the sexual satisfaction of their partner. And evidence shows that women with male partners with ED do have an impact on men's inclination to seek and maintain treatment for this condition.[167] The long-term use of ED therapy is more likely when the man's partner is both involved and supportive of the decision to seek and use the therapy and when treatment successfully increases her sexual satisfaction.

PDE5 inhibitors have added an interesting dynamic to many couple's sex lives. In spite of the fact that many men have a positive response to this medication, less than half of all PDE5 prescriptions are actually refilled.[168] This is, in part, due to the fact that after having lost an intimate connection, sexual reconnection can be difficult. In one study that looked at continuation of use for PDE5 inhibitors, men seldom reported that "partner issues" were a significant reason for stopping. In the same study, for a number of women, "partner issues," meaning a range of problems from separation to alcohol abuse, lack of communication, and lack of confidence, or fear of failure, were significant reasons for discontinuation, although discontinuation did not mean that the couples were no longer sexually active.[169] Successful treatment of ED, however, has been shown to improve quality of life for both men with ED and their female partners.[170,171]

CLINICAL NOTES

- There is much overlap among the female sexual dysfunctions. Men's sexual dysfunctions tend to be more defined.
- Women experience more emotional complaints about sex than men do. Women place great importance on thoughts and feelings during sex. Men are more focused on performance issues.
- For women, lack of spontaneous sexual desire is considered within the realm of normal. Lack of spontaneous desire in men is typically considered a dysfunction.
- Women's arousal is more subjective—there is a poor correlation between her subjective feeling of arousal and her body's response to sexual stimuli.
- Women's sexuality is more fluid—her preferences are more amenable to change with time than men's.
- Research consistently shows that patients have sexual concerns they want to discuss with their doctors.
- Asking a few general, open-ended questions will invite this type of dialogue without putting your patient on the spot or making them feel uncomfortable.
- A woman's sexual response is intricately tied to all aspects of her life. When any aspect of her life is out of balance, her sexual response may be affected.
- Common medications, including antidepressants and birth control pills, can interfere with any aspect of a woman's sexual functioning.
- Many of the ways people cope and relieve stress can negatively impact sexual functioning, such as overreliance on food, alcohol, or sedentary activity.
- Dyspareunia and vaginismus are multidetermined, heterogeneous disorders that require a multimodal treatment approach.
- Dyspareunia is painful intercourse. Vaginismus is a tightening of the muscles in the outer third of the vagina, making intercourse difficult or impossible.
- It is necessary to differentiate the sexual pain disorders from provoked vestibulodynia so as to accurately orchestrate care.
- Consider pelvic floor physical therapy, lubricants, and dilators for the sexual pain patient.
- HSDD is the most common female sexual dysfunction. Unless it is accompanied by personal distress on the part of the patient, lack of spontaneous desire is not considered a problem.
- HSDD is complex and requires a multimodal treatment approach, typically involving a variety of practitioners.
- The HSDD patient must expect to be a major participant in her treatment. Do not set yourself up to "fix" or "heal" your patient without the patient's combined efforts.
- Consider off-label use of testosterone supplementation or bupropion for the HSDD patient.
- FSAD often co-occurs with HSDD.
- FSAD is difficult to diagnose accurately because it relies almost exclusively on patient self-report
- Off-label use of bupropion or PDE5 inhibitors have had mixed results with the FSAD patient. Treatment often involves a nonpharmacologic approach.
- If postmenopausal, consider estrogen therapy for the FSAD patient.
- Masturbation with a vibrator is the basic treatment for primary orgasmia.
- The effect of PDE5 inhibitors or bupropion has been modest with the patient with orgasmic disorder.
- If postmenopausal, consider estrogen therapy for the FOD patient.

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Appendix 9.A
Websites for More Information

1. ISSWSH: International Society for the Study of Women's Sexual Health: www.isswsh.org
2. SIECUS: Sexuality Information and Education Council of the United States: www.siecus.org
3. SSSS: Society for the Scientific Study of Sexuality: www.sexscience.org
4. AASECT: American Association for Sex Educators, Counselors, and Therapists: www.aasect.org
5. NVA: National Vulvodynia Association: www.nva.org
6. NAMS: The North American Menopause Society: www.menopause.org
7. Female Sexual Dysfunction Online: www.femalesexualdysfunctiononline.org
8. Nurture Your Nature: www.nurtureyournature.org
9. Society for Sex Therapy and Research: www.sstarnet.org
10. The Women's Sexual Health Foundation: www.twshf.org
11. The Kinsey Institute for Research in Sex, Gender, and Reproduction: www.kinseyinstitute.org

Appendix 9.B
Recommended Readings

Sexual Dysfunction

1. For Women Only: A Revolutionary Guide to Overcoming Sexual Dysfunction and Reclaiming Your Sex Life by Jennifer Berman and Laura Berman.
2. Making Love the Way We Used to or Better: Secrets to Satisfying Midlife Sexuality by Alan Altman and Laurie Asher.
3. The New Love and Sex After 60 by Robert Butler and Myrna Lewis.

Hypoactive Sexual Desire Disorder

4. Mating in Captivity by Esther Perel
5. The Dark Side of Intimate Relationships by Douglas and Naomi Moseley
6. How Can I Get Through To You? by Terrence Real
7. Sex Smart: How Your Childhood Shaped Your Sexual Life and What to Do About It by Aline Zoldbrod

Orgasmic Disorder

8. For Yourself: The Fulfillment of Female Sexuality by Lonnie Barback
9. Becoming Orgasmic: A Sexual and Personal Growth Program for Women by Julia Heiman and Joseph Lopiccolo
10. Getting the Sex You Want: A Woman's Guide to Becoming Proud, Passionate, and Pleased in Bed by Sandra Leiblum and Judith Sachs

Painful Sex

11. Secret Suffering: How Women's Sexual and Pelvic Pain Affects Their Relationships by Bilheimer and Echenberg

Sexual Arousal Disorder

12. The Complete Idiot's Guide to Tantric Sex by Judy Kuriansky
13. Illustrated Manual of Sex Therapy by Helen Singer Kaplan

Cancer and Sex

14. Women Cancer Sex by Anne Katz

Erectile Dysfunction

15. Coping with Erectile Dysfunction by Metz and McCarthy
16. Coping with Premature Ejaculation by Metz and McCarthy
17. Male Sexuality by Michael Bader

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CHAPTER 10

Office Management of Endometriosis

Jennifer F. Knudtson and Robert S. Schenken

Endometriosis is the presence of endometrial glands and stroma outside the uterine cavity and musculature. These ectopic endometrial implants can occur anywhere in the body but are usually found in the pelvis. Endometriosis has a wide spectrum of symptoms. Women usually present with pelvic pain, with severity of the pain ranging from minimal to debilitating, dyspareunia, and infertility. They may present with a pelvic mass. Endometriosis is a chronic, estrogen-dependent disorder that can have a profound impact on a woman's life affecting her physical, emotional, and social well-being.

The actual prevalence in the population is unknown, but it is estimated to be about 6 to 10% of reproductive age women in all ethnic and social groups.[1] The prevalence of pelvic endometriosis is 1% in women undergoing major surgery for all gynecologic indications and 30 to 60% in women undergoing diagnostic laparoscopy for pelvic pain.[2–4] Approximately two-thirds of teenagers undergoing laparoscopy for pelvic pain not responsive to treatment have endometriosis.[5] One-third of women undergoing laparoscopy for infertility are found to have endometriosis.[6] In the United States in 2002, the direct treatment cost of endometriosis was around $18.8 billion, and combination of direct and indirect cost was $22 billion.[7]

PATHOGENESIS

Multiple theories have been proposed to explain the histogenesis of endometriosis.[6] No one theory can explain the pathogenesis completely, and it is possible that more than one source or pathway leads to the development of endometriosis. The most widely accepted theory is retrograde menstruation or implantation theory, also known as Sampson theory, where endometrial fragments shed during menstruation are transported retrograde through the fallopian tubes and then implant in the pelvis. The direct transplant theory explains the development of endometriosis in a scar after cesarean section, vaginal repair, or other pelvic surgery. The coelomic metaplasia theory is derived from the embryologic basis that all pelvic organs develop from the spontaneous or induced metaplastic change in mesothelial cells that line the coelomic (peritoneal) cavity. It proposes that the lining of the abdominal cavity contains undifferentiated cells with the ability to differentiate into endometrial cells. Evidence also indicates that endometriosis can spread outside the pelvis through vascular and lymphatic channels.

Anatomy, altered immunity, and genetics influence the development of endometriosis. Anatomic differences in the pelvis, which increase reflux through the fallopian tubes, increase the chance of endometriosis. For example, endometriosis has a higher incidence in females with müllerian anomalies, which result in outflow tract obstruction.[8] However, women with endometriosis do not have a higher incidence of retrograde menstruation compared to women without endometriosis. Although almost all women have retrograde menstruation, not all women develop the disease. The development of endometriosis may depend on alterations in the immune response that recognizes and eliminates refluxed endometrial fragments as well as increased ability of the ectopic endometrial cells to adhere and invade into the peritoneal cavity or other surfaces.[9,10] Endometriotic implants are associated with an increased production of cytokines, prostaglandins, and growth factors, which lead to increased proliferation of ectopic implants, enhanced local angiogenesis, and the attraction of leukocytes to the sites of inflammation.[11] Genetics may also play a role in the development of endometriosis. The first-degree relatives of women with endometriosis have a 7% likelihood of developing or having the disease compared to a 1% likelihood in unrelated women.[12] Numerous studies have looked for specific genes that predispose to the development of endometriosis, but the exact genetic cause is unclear.[13]

The stem cell theory of endometriosis centers on the idea that mesenchymal stem cells that are derived from bone marrow can differentiate into endometrium and endometriosis.[14] There is evidence that in women who have undergone bone marrow transplants, the endometrium in these women contains a substantial number of donor-derived endometrial cells.[14] It is possible that stem cells that are derived from the bone marrow (even in women who have not been given a bone marrow transplant) reside in the endometrium and may reflux during retrograde menstruation and cause

endometriotic implants just as endogenous endometrial cells may. Further evidence demonstrates that endometriotic implants are populated by bone marrow–derived stem cells. This stem cell theory would also explain cases of endometriosis at sites outside the peritoneal cavity; endometriosis at distant sites may arise from stem cells.

Women with endometriosis also have an increased risk of malignancy and autoimmune diseases. One study of women discharged from the hospital with a diagnosis of endometriosis suggested an increased risk of developing breast, ovarian, and hematopoietic cancers in the future.[15] Rarely, adenocarcinoma may also develop from endometriotic implants.[16] Endometriosis and ovarian cancer share certain risk factors such as early menarche (before age 11 years), shorter cycle lengths (less than 27 days), and lower parity.[17] Studies show that the relative risk of ovarian cancer appears to be increased in women with a long history of endometriosis, although the magnitude of the increased risk is not clear.[18,19] The risk of ovarian cancer appears to be highest for women with endometriosis and primary infertility, although this risk may be reduced with the use of oral contraceptive pills.[20,21] Screening women with endometriosis for ovarian cancer is not recommended however because the incidence is low, and importantly, there is no effective screening test. There is also no evidence that removing sites of endometriosis will decrease the risk of ovarian cancer.

Autoimmune diseases such as rheumatoid arthritis and systemic lupus along with hypothyroidism, fibromyalgia, chronic fatigue syndrome, and asthma are also more common in patients with endometriosis.[22]

PATHOLOGY

Endometriosis is most commonly found in the ovaries, followed by the anterior and posterior cul de sac, posterior broad ligaments, uterosacral ligaments, uterus, fallopian tubes, and round ligaments. Both ovaries are involved in about 33% of cases. The left side of the pelvis and left ovary are more frequently affected than the right, possibly because the presence of the sigmoid colon decreases peritoneal fluid movement. Gastrointestinal involvement is the most frequent extragenital site of endometriosis, occurs in 5% of cases, and most commonly affects the sigmoid colon.[23] The urinary tract is the third most commonly involved system with superficial endometriotic lesions found in the bladder, followed by the ureter. Other less common sites include the cervix, vagina, cecum, ileum, umbilicus, and inguinal canals. Rare cases have found endometrial implants in the lung, diaphragm, breast, pancreas, liver, gallbladder, kidney, urethra, vertebrate, bone, nervous system, and extremities.[6]

Microscopically, endometriosis has the characteristics of the uterine endometrium including glands and stroma. The endometriotic lesions also contain fibrosis, hemosiderin-laden macrophages, and blood. The lesions can be superficial or invasive into the ovary or retroperitoneum.

The visual appearance and size of endometrial lesions is extremely variable. Lesions can appear as the bluish black "powder burn" lesions due to the hemosiderin deposits and as whitish opacifications, translucent blebs, raised flame-like patches, or reddish/reddish blue irregularly shaped islands. These lesions are often seen with peritoneal surfaces that appear scarred (see Figs. 10.1 through 10.4 for pictures of endometriosis).

Ovarian implants can present superficially or as cyst-like structures called endometriomas. Endometriomas, often referred to as chocolate cysts, contain blood, fluid, and endometrial fragments. They are frequently densely adherent to nearby structures.

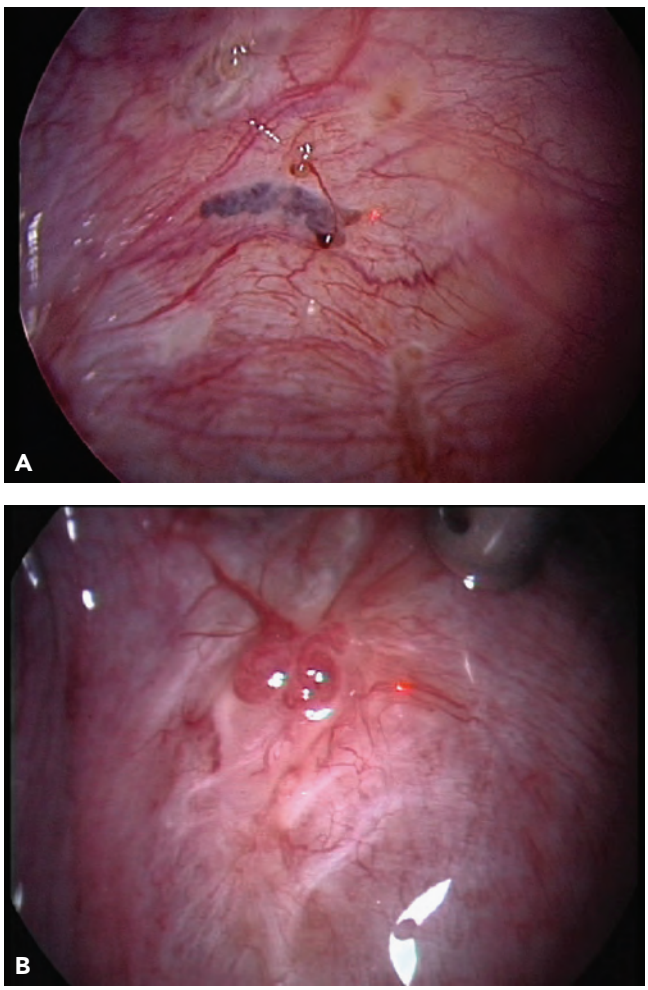


FIGURE 10.1 Typical and subtle endometriotic lesions on peritoneum. **A:** Typical black-puckered lesions with hypervascularization and orange polypoid vesicles. **B:** Red polypoid lesions with hypervascularization. (Photographs kindly donated by Dr. Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium. From Berek JS, ed. *Berek & Novak's Gynecology*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

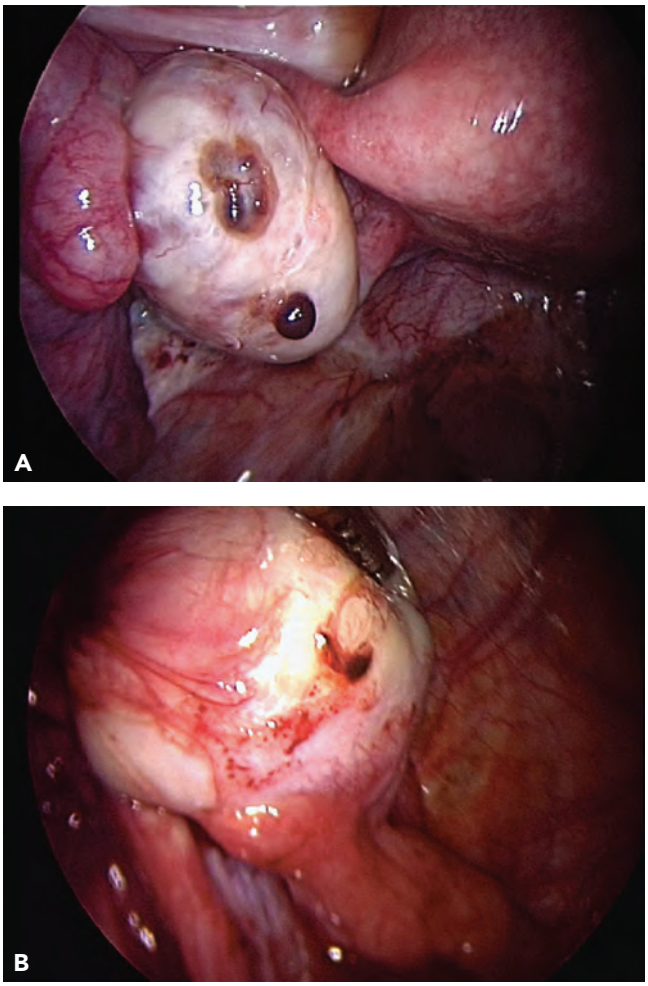


FIGURE 10.2 Ovarian endometriosis. **A:** Superficial ovarian endometriosis. **B:** Superficial ovarian endometriosis and endometrioma laparoscopic image prior to adhesiolysis. (Photographs kindly donated by Dr. Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium. From Berek JS, ed. *Berek & Novak's Gynecology*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

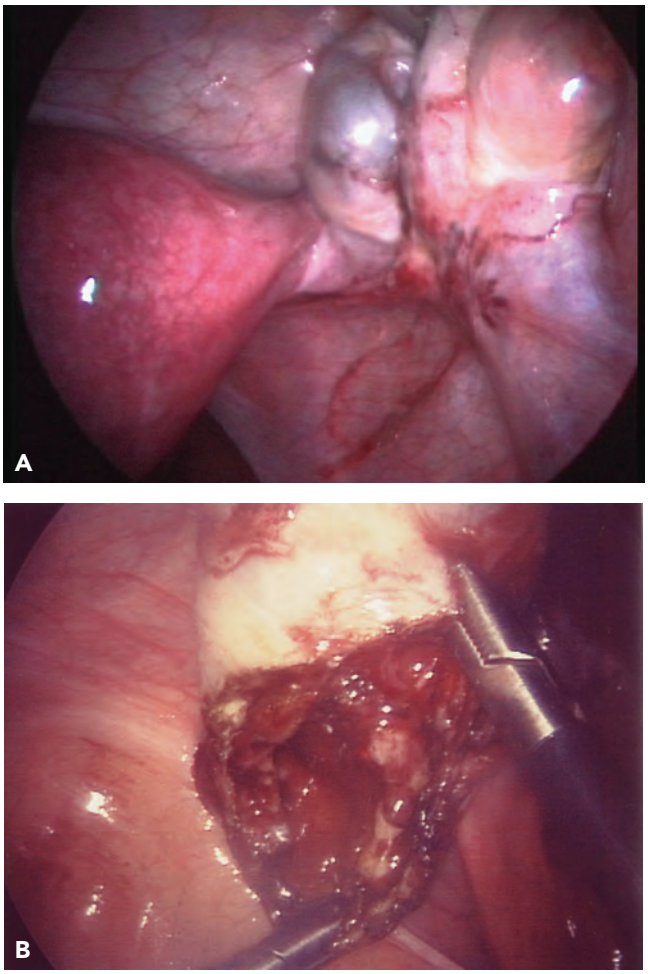


FIGURE 10.3 **A:** Laparoscopic image of uterus and right ovary with dark endometrioma. **B:** Ovarian endometriotic cystectomy. (From Berek JS. *Berek & Novak's Gynecology*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

DIAGNOSIS

The diagnosis of endometriosis is most often made in reproductive age women. It is rarely found in prepubertal girls and only occasionally diagnosed after menopause. Clinical manifestations of endometriosis include pelvic pain, infertility, and adnexal masses. The most common symptom is pain. Pelvic pain symptoms usually include secondary dysmenorrhea, which typically begins before onset of menses, and dyspareunia, which is increased with deep penetration and prior to menses. Women may also experience noncyclic pelvic pain, abdominal cramps, low back pain, and abnormal menstrual bleeding. Another presenting complaint is infertility. If there is bowel involvement, endometriosis may present as dyschezia, constipation or diarrhea, rectal bleeding, and bloating. If the bladder is involved, there may be dysuria or hematuria. It is important to appreciate that the stage of endometriosis *does not* correlate with the severity of symptoms. The location and depth of implantation of the ectopic endometrium may play a role in symptomatology. Pain with defecation during menses and severe dyspareunia are the most predictable symptoms of deeply infiltrating endometriosis.[24]

When considering the diagnosis of endometriosis for pelvic pain, other causes of pelvic pain need to be investigated. Adenomyosis, leiomyomata, pelvic inflammatory disease, ovarian or tubal masses, pelvic floor dysfunction, and pelvic adhesions are reproductive conditions that may also cause chronic pelvic pain. Common nongynecologic etiologies of pelvic pain are gastrointestinal, musculoskeletal, neurologic, psychological, or urinary system disorders. Patients may also present with irritable bowel syndrome, inflammatory bowel disease, or interstitial cystitis (see Table 10.1 for symptoms of endometriosis).

Although the average age at diagnosis is 28 years, up to 67% of adult women with endometriosis note that their symptoms started before the age of 20 years.[25] Among adolescents, 47% of those with chronic pelvic pain that

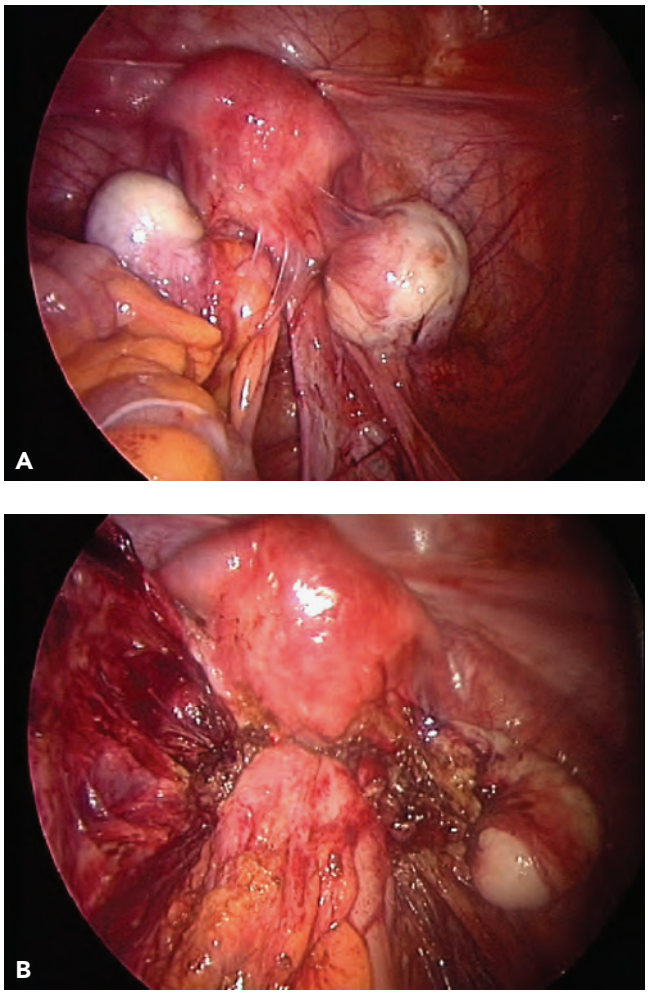


FIGURE 10.4 Laparoscopic excision of deep endometriosis from the cul de sac. **A:** Extensive endometriosis with deep nodule at the right uterosacral ligament masked by adhesions. **B:** Deep nodule is still present in dense adhesion between rectum and uterosacral ligaments. (Photographs kindly donated by Dr. Christel Meuleman, Leuven University Fertility Center, Leuven University Hospitals, Leuven, Belgium. From Berek JS. *Berek & Novak's Gynecology*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

TABLE 10.1 Symptoms of Endometriosis

Symptom	Percentage of Women With Endometriosis With This Presenting Symptom	Other Possible Diagnoses or Confounders
Dysmenorrhea	79	Adenomyosis, primary dysmenorrhea
Pelvic pain	69	Irritable bowel syndrome, adhesions, neuropathic pain
Dyspareunia	45	Vaginal atrophy, vaginal dryness, vulvar disorders, adhesions, neuropathic pain, adenomyosis
Bowel symptoms	36	Constipation, inflammatory bowel disease; irritable bowel syndrome, hemorrhoids
Bowel pain	29	Anal fissures, hemorrhoids
Infertility	26	Unexplained subfertility or female/male/combination factor infertility
Ovarian mass or tumor	20	Hydrosalpinx; benign ovarian cyst
Dysuria	10	Cystitis
Other urinary problems	6	Interstitial cystitis

Adapted from Sinaii N, Plumb K, Cotton L, et al. Differences in characteristics among 1,000 women with endometriosis based on extent of disease. *Fertil Steril.* 2008;89:538–545.

have laparoscopy are found to have endometriosis, and among adolescents with chronic pelvic pain that do not respond to oral contraceptives or NSAIDs who undergo laparoscopy, endometriosis is found in 50 to 70% of cases. Adolescents with endometriosis often have both acyclic and cyclic pain. The least common pain presentation among adolescents is isolated cyclic pain, which is in contrast to adults with endometriosis who commonly have cyclical pain.

Endometriosis is sometimes difficult to diagnose based on clinical manifestations alone, but physical findings are variable and depend on the location and size of the implants. Frequently, there are no abnormal findings on physical examination. The most common findings are tenderness in the posterior cul de sac or nodularity on palpation of the uterosacral ligaments, although this latter finding is rarely found in adolescents. There may be thickening of the uterosacral ligaments, pain with uterine movement, or tender nodules in the posterior cul de sac or rectovaginal septum. Other findings include ovarian cysts, a nonmobile uterus secondary to adhesions, or an obliterated cul de sac.

The gold standard to diagnosis of endometriosis is laparoscopy, which allows for direct visualization of the implants. It is best to avoid laparoscopy during or within 3 months of hormonal treatment because this may lead to underdiagnosis of the disease. Prominent pelvic vessels may suggest pelvic congestion syndrome, which some argue is a cause of chronic pelvic pain but is not a sign of endometriosis. In 2 to 4% of women with endometriosis, the appendix may be involved so this should be visualized during laparoscopy. A negative laparoscopy is highly reliable for excluding endometriosis, although it may miss occult microscopic implants, but visual diagnosis alone is associated with a high rate of error in diagnosis.[26] Biopsy of suspicious areas are suggested, particularly when the appearance of the implants is atypical.

There are no blood tests or imaging studies to make the definitive diagnosis. Imaging studies, such as ultrasonography or magnetic resonance imaging, may be useful when an adnexal mass is present for a presumptive diagnosis of an endometrioma. Transvaginal sonography may be helpful in detecting deeply infiltrating endometriosis of the rectum or rectovaginal septum, and water contrast in the rectum may help determine if the lesions are infiltrating the bowel.[27,28] CA-125, a cell surface antigen used for monitoring epithelial ovarian

cancer, is elevated in endometriosis and has been found to have a diagnostic specificity greater than 90% and sensitivity of 50%.[29] In one series of 685 women undergoing surgery for endometriosis, the mean serum CA-125 levels in stage I, II, III, and IV disease were 19, 40, 77, and 182 IU/mL, respectively.[30] Levels greater than 100 IU/mL were usually associated with extensive adhesions or a ruptured endometrioma. Other conditions that increase CA-125 levels are pelvic inflammatory disease, leiomyomas, pregnancy, cirrhosis, and appendicitis (see Table 10.2 for a listing of conditions associated with elevated levels of CA-125).

The American Society for Reproductive Medicine classification system for endometriosis was first introduced in 1979 to correlate pain and infertility with disease severity. It was then revised in 1985 and again in 1996, and despite its limitations, it is the most widely accepted staging system. The system assigns points for the size and location of the lesions and any associated adhesions. It does not correlate well with pain, dyspareunia, or infertility. Its primary value lies in providing a uniform record of operative findings and quantification of disease, thus allowing for a comparison between various therapies.

TABLE 10.2 Conditions Associated With Elevated Serum CA-125

Benign Gynecologic Conditions
- Benign ovarian neoplasms
- Functional ovarian cysts
- Endometriosis
- Meigs syndrome
- Adenomyosis
- Uterine leiomyomas
- Pelvic inflammatory disease
- Ovarian hyperstimulation
- Pregnancy
- Menstruation

Nongynecologic Conditions
- Cirrhosis and other liver disease
- Ascites
- Colitis
- Diverticulitis
- Appendiceal abscess
- Tuberculosis peritonitis
- Pancreatitis
- Pleural effusion
- Pulmonary embolism
- Pneumonia
- Cystic fibrosis
- Heart failure
- Myocardiopathy
- Myocardial infarction
- Pericardial disease
- Renal insufficiency
- Urinary tract infection
- Recent surgery
- Systemic lupus erythematosus
- Sarcoidosis

Gynecologic Malignancies
- Epithelial ovarian
- Fallopian tube
- Primary peritoneal
- Endometrial

Nongynecologic Cancers
- Breast
- Colon
- Liver
- Gallbladder
- Pancreas
- Lung
- Hematologic malignancies

Data from Baumah P. Benign conditions associated with raised serum CA-125 concentrations. *J Surg Oncol.* 2000;75:264–265; Miralles C, Orea M, España P, et al. Cancer antigen 125 associated with multiple benign and malignant pathologies. *Ann Surg Oncol.* 2003;10:150–154; Moss EL, Hollingworth J, Reynolds TM. The role of CA125 in clinical practice. *J Clin Pathol.* 2005;58:308–312.

The staging is performed surgically where all the lesions can be visualized. The total score determines the disease category of minimal (I), mild (II), moderate (III), or severe (IV). There is some evidence that endometriotic lesions are innervated and that pain may be related to nerve density in the lesions which, in turn, seems to correlate with the histologic type of lesion, depth of invasion, and proximity of nerves to the lesions[31] (see Fig. 10.5 for the revised American Society for Reproductive Medicine classification of endometriosis).[32]

TREATMENT

The treatment of endometriosis depends on the severity of symptoms, extent of disease, location of disease, age of patient, and desire for future fertility. There are multiple treatments from medical to surgical to homeopathic. Despite extensive research, the optimal management of endometriosis remains controversial. Therapy is aimed at treating the patient's symptoms, and treatment plans are individualized. The discussions of therapies that follow will focus on the management of endometriosis-related pain, infertility, and endometriomas, respectively. Regardless of the reason(s) for treatment, the side effects of medications, complication rates of surgery, and the costs of interventions of possible treatments are important management considerations.

Treatment of Pelvic Pain

There are many theories of the etiology for the pelvic pain including different nerve irritations, inflammatory reactions, or bleeding within the implants.[33] Most studies have found increased proinflammatory cytokines and growth factors in endometriosis that are closely related to pain sensation, which may explain why even minimal endometriosis may cause severe pain. There is some evidence that the peripheral nerve fibers supplying endometriotic implants may sensitize spinal segmental neurons and eventually, the central nervous system as well. This would result in an exaggerated central nervous system response to pain, even if lesions were ablated.[34,35] Multiple treatments are available for endometriosis-associated pelvic pain, and the multidimensional symptomatology of this disease warrants a multidisciplinary approach to treatment. Treatment regimens for pain usually begin with trials of medical treatments when the clinical suspicion for endometriosis is high and no pelvic mass is appreciated. Medical therapy for endometriosis aims to control pain and suppress estrogen production based on the premise that a hypoestrogenic environment will inhibit endometrial growth and promote regression of the disease. The main disadvantage to this approach is that symptoms usually recur once treatment is stopped. Overall, the available hormonal therapies used appear to have similar effectiveness in treating chronic pelvic pain. For some patients, surgery is the initial step in the diagnosis and treatment

American Society for Reproductive Medicine
Revised Classification of Endometriosis

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 _____

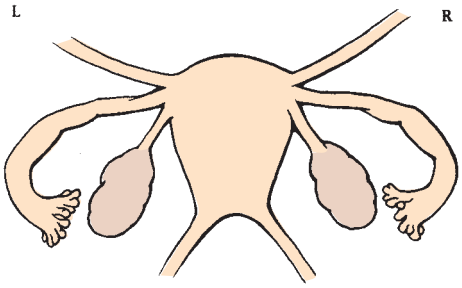
PERITONEUM	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CUL-DE-SAC OBLITERATION	Partial	Complete	
		4	40	
OVARY	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	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: _____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and/or Ovaries

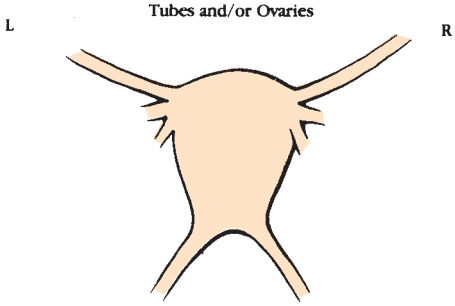


FIGURE 10.5 Revised American Society for Reproductive Medicine classification. (From Schenken R, Guzick D. Revised endometriosis classification: 1996. *Fertil Steril*. 1997;67:815–816.)

of endometriosis. Additional surgery may be indicated in women with known severe disease who desire fertility, and assisted reproductive techniques may follow surgery. No studies have directly compared surgical versus medical treatment for endometriosis (see Table 10.3 for a list of treatment options for endometriosis).

Expectant Management

Although endometriosis is a chronic disease with a propensity for relapse, a woman with minimal or mild endometriosis can be managed expectantly if she is asymptomatic. These patients are usually diagnosed incidentally during a surgery for another reason. Although the natural course of endometriosis is not well known, long-term studies would indicate that expectant management will be associated with disease progression in 29 to 44% of patients, disease regression in 22 to 29% of women, and no change in 33 to 42% of women with this disease.[36,37] Overall then, it would appear that the distribution of change is roughly divided into thirds among these possibilities. For women not currently interested

TABLE 10.3 Treatment Options for Endometriosis-Associated Pain

Expectant management
Medical therapy
Analgesics (NSAIDs)
Combined estrogen/progesterone
Progestins (oral, parenteral, implants, IUDs)
Danazol
Gonadotropin-releasing hormone (GnRH) agonists
Aromatase inhibitors
Surgical therapy
Conservative
Laparoscopy with surgical excision of lesions
Laparotomy with surgical excision of lesions
Definitive
Hysterectomy with removal of ovaries
Hysterectomy without removal of ovaries
Combination therapy
Medical therapy before surgery
Medical therapy after surgery
Investigational

NSAIDs, nonsteroidal anti-inflammatory drugs; IUDs, intrauterine devices.

TABLE 10.4 Medical Therapy Options and Dosages for Dysmenorrhea

Drug	Dosing
Acetic acids	
Indomethacin	25 mg tid
Tolmetin	400 mg tid
Sulindac	200 mg bid
Diflunisal	1000 mg initially, then 500 mg every 12 h
Diclofenac	75 mg bid
Etodolac	400 mg every 6–8 h (maximum dose 1200 mg in 24 h)
Ketoralac	10 mg every 4–6 h (maximum dose 40 mg in 24 h)
Propionic acids	
Ibuprofen	400 mg every 6 h
Naproxen	500 mg initially, then 250 mg every 6–8 h (maximum dose 1250 mg every 24 h)
Naproxen sodium	550 mg initially, then 275 mg every 6–8 h
Fenoprofen calcium	200 mg every 4–6 h
Ketoprofen	75 mg tid
Fenamates	
Mefenamic acid	500 mg initially, then 250 mg every 4 h
Meclofenamate	100 mg initially, then 50–100 mg every 6 h
Oxicans	
Piroxicam	20 mg every 24 h

in pregnancy, starting a combination oral contraceptive may be beneficial regardless of symptoms to prevent further progression of disease.

Medical Therapy

Most of the medical therapies used to treat endometriosis are aimed at the key components of the disease process: retrograde menstruation, estrogen dependence, progesterone resistance, inflammation, and angiogenesis. NSAIDs are used to target inflammation (see Table 10.4 for medical therapy options for dysmenorrhea). Endometrial implants contain estrogen, androgen and progestin receptors, and hormonal treatments such as contraceptive steroids, progestogens, and antiprogestogens, GnRH agonists and danazol target these receptors and their ligands.[38] Although many of these therapies effect a decrease in estrogen, it is important to note that shutting down the ovary alone will not eliminate estrogen production; other sources include adipose tissue, in the ectopic and eutopic endometrium in women with endometriosis, certain areas of the brain, and even the dorsal root ganglia help contribute to the production of estrogen.

Women presenting with pelvic pain and the suspected diagnosis of endometriosis can be started on empiric medical treatment prior to diagnosis by laparoscopy after other gynecologic sources of pain have been excluded.[39] Although 80 to 90% of patients will improve with medical therapy, these interventions do not enhance fertility or treat endometriomas. If infertility or a pelvic mass is involved, a trial of medical therapy is not recommended (see Table 10.5 for drugs used in the treatment of endometriosis-associated pain).

Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in treating primary dysmenorrhea. By blocking cyclooxygenase (COX)-1 and COX-2 enzymes, they inhibit prostaglandin production and thus decrease the pain of dysmenorrhea. NSAIDs do not keep endometriosis from progressing. No large, randomized controlled trials have evaluated the use of NSAID analgesics for endometriosis. The Cochrane Review reports there is limited evidence to show that NSAIDs are effective, and no evidence shows one NSAID to be more effective than another.[40] Common side effects are gastrointestinal symptoms. NSAIDs are affordable, available, and tolerable. A 3-month trial of NSAIDs in women with minimal or mild disease is a reasonable approach.

Combined Estrogen and Progesterone

Hormonal treatment of endometriosis is aimed at inducing amenorrhea or diminished menstruation, creating a relatively hypoestrogenic environment to inhibit endometrial growth and promote disease progression. Unfortunately, symptoms often recur once therapy is stopped. Combination contraceptives initially induce decidualization in eutopic and ectopic endometrium, followed later by atrophy and may help delay progression of disease.[41]

Combination oral contraceptive pills (OCPs) are used in women with no current interest in fertility and who have minimal to mild disease. There are few randomized

TABLE 10.5 Drugs Used for the Treatment of Endometriosis

Class	Drug (Selected Listing)	Dosing	Side Effects
Androgen	Danazol[a]	100–400 mg orally bid 100 mg vaginally QD	Weight gain, fluid retention, breast atrophy, acne, oily skin, hot flushes, hirsutism, and unfavorable changes in the lipid profile
Aromatase inhibitor	Anastrozole[b] Letrozole[b]	1 mg orally QD 1.5 mg orally QD	Ovarian stimulation in premenopausal women
Estrogen-progestin combinations	OCP with ≤35 mcg ethinyl estradiol[a] Transdermal contraceptive patch Vaginal contraceptive ring	Continuously for 3 mo with 1 wk hormone-free interval or just continuously	Mild nausea, vomiting
Gonadotropin-releasing hormone agonist	Goserelin[a,b] Leuprolide depot[a,b] Nafarelin[a,b]	3.6 mg SC monthly (10.8 mg IM every 3 mo) 3.75 mg IM monthly (11.25 mg IM every 3 mo) 200 mcg intranasally bid	Symptoms of a hypoestrogenic state (hot flushes, mood irritability, vaginal dryness, sleep disturbances, and decreased bone mineral density)
Gonadotropin-releasing hormone antagonist	Cetrorelix	3 mg SC weekly	GnRH antagonists are commonly associated with hormonal side effects such as hot flushes, headache, nausea and weight gain. When used in fertility treatment, they can also be associated with abdominal pain and ovarian hyperstimulation. Subcutaneously administered agents are also associated with injection-site reactions, and abarelix has been linked with immediate-onset systemic allergic reactions.
Progestin	Depo-SubQ Provera 104[a] Dienogest[c] Etonogestrel-releasing implant Levonorgestrel-releasing IUS Medroxyprogesterone acetate Norethindrone acetate[a]	104 mg/0.65 mL SC every 3 mo 2 mg daily 1 for 3 yr 1 for 5 yr 30 mg orally QD for 6 mo, then 100 mg IM every 2 wk for 2 mo, then 200 mg IM monthly for 4 mo 5 mg QD	Breakthrough bleeding, breast tenderness, weight gain. Some have unfavorable effects of bone mineral density and lipid profile; some have androgenic side effects.
Prostaglandin inhibitors	Acetaminophen Aspirin Ibuprofen Indomethacin Naproxen Ketorolac IV/IM Oral ketorolac Celecoxib	1000–4000 mg/d (maximum 4000 mg/d) 1000–4000 mg/d 1200–2400 mg/d 75–150 mg/d 500–1000 mg/d 30–60 mg IV/IM initially, then 15–30 mg q6h bolus IV/IM. Short-term use only: 3–5 d 60 mg/d. Limit use to not more than 14 d. 200–400 mg/d	Unfavorable gastrointestinal side effects

bid, twice daily; QD, daily; OCP, oral contraceptive pill; SC, subcutaneously; IM, intramuscularly; GnRH, gonadotropin-releasing hormone; IUS, intrauterine system; IV, intravenously.
[a]FDA approved for endometriosis.
[b]With add-back, that is, norethindrone acetate 5 mg daily plus vitamin D 800 IU daily with 1.25 g calcium daily.
[c]Dienogest is not available in the United States as an individual drug. It is found in the oral contraceptive Natazia (Bayer HealthCare Pharmaceuticals; estradiol valerate/dienogest).

controlled trials on OCPs for endometriosis. All, including the Cochrane Review, have found OCPs to be more effective than placebo and as effective as GnRH analogues and danazol.[42–44] Low-dose OCPs have also been shown to decrease endometriosis pain symptoms.[43] Side effects from OCPs include nausea, breast tenderness, and irregular vaginal bleeding. Contraindications should be reviewed prior to prescribing especially any history of thromboembolic events. There is no conclusive evidence that one OCP formulation is better than another.

Continuous OCPs are a reasonable option to either start with or to use when cyclic OCPs do not control their pain.[45] Typically, a continuous OCP regimen is 12 weeks (four packs) of active pills continuously then one hormone-free week. When on continuous OCPs, patients may experience increased breakthrough bleeding that may be corrected by adding estrogen supplement or returning to a cyclic regimen. OCPs are commonly combined with NSAID treatment. Other combined hormonal treatments include the NuvaRing and the Ortho Evra patch, which both provide pain relief.[46] If after 3 to 6 months of combined hormonal treatment there is no relief, another treatment modality should be pursued.

Progestins

Endometriotic lesions may be resistant to decidualization and atrophy. Progestins have anti-inflammatory, antiangiogenic, and immunomodulatory effects and can be effective in controlling the underlying processes of pain in endometriosis. They decrease pituitary gonadotropins, induce anovulation, and thus create a relatively hypoestrogenic environment. When they are used at appropriate doses, they yield partial or complete pain relief in more than 80% of women with endometriosis.[47,48] Their efficacy in eliminating implants and recurrence is not well known, although one study found that about half of symptomatic patients experience a recurrence upon discontinuation.[48] Overall, they have a good tolerability profile and are affordable. Side effects include irregular bleeding, nausea, weight gain, breast tenderness, depression, and fluid retention. Breakthrough bleeding may occur and can be treated with micronized estradiol (2 mg daily) or conjugated estrogen (1.25 mg daily) for 7 to 14 days. There are multiple options for progestin treatment including oral agents, intramuscular injections, an intrauterine device, and subdermal implants (see Table 10.6 for a listing of progestins used in the treatment of endometriosis-associated pain).

Depot medroxyprogesterone acetate (DMPA or Depo-Provera) is an intramuscular or subcutaneous progestin given every 3 months in doses of 104 to 150 mg to prevent pregnancy. The subcutaneous injection has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of endometriosis. In randomized trials, it is as effective as leuprolide and danazol in reducing dysmenorrhea, pelvic pain, pelvic tenderness, and dyspareunia.[47,48] Breakthrough bleeding, weight gain, mood changes, depression, irritability, and amenorrhea are common side effects of DMPA. This may be managed with a 10- to 14-day course of low-dose estrogen.

Long-term use of DMPA or high-dose oral medroxyprogesterone acetate (MPA) has been associated with reduced bone mineral density, but this loss is not as pronounced as that seen with GnRH agonists.[49] Once the progestin agents are stopped, bone density generally improves although symptoms of endometriosis may also recur. Supplemental calcium and vitamin D are recommended for women using DMPA or high-dose MPA.

There are a variety of oral progestin agents such as MPA, norethindrone acetate, megestrol, and dienogest that may be used to treat endometriosis. The use of high-dose norethindrone acetate (5 mg orally every day, with a maximum dose of 15 mg daily), a 19-nortestosterone progestin, is FDA approved for the treatment of endometriosis-associated pain in conjunction with leuprolide. It is effective even with rectovaginal endometriosis.[50] Although not FDA approved for this indication, MPA (10 mg twice a day or three times a day) is also used to treat the pain of endometriosis. Long-term use of norethindrone acetate or MPA may result in bone loss as well as significant declines in high-density lipoprotein (HDL) cholesterol and increases in low-density lipoprotein (LDL) cholesterol and triglycerides. Side effects such as weight gain, bloating, and mood swings often occur and are common reasons patients discontinue their use.

There is some data on the use of the levonorgestrel-releasing intrauterine system (LNG-IUS) that shows symptom relief comparable to GnRH agonists, even in patients with advanced endometriosis although close to 44% of patients discontinued use because of irregular bleeding, persistent pain, or weight gain.[51–53] In other trials, the subdermal implantable progestin, etonogestrel, demonstrated significant reduction in the intensity of pain associated with endometriosis, including dyspareunia, dysmenorrhea, and nonmenstrual pelvic pain that was comparable to DMPA.[53–55] Use of these progestins does not significantly affect bone mineral density or lipid parameters.

Danazol

Danazol is a 17-ethinyl testosterone derivative that acts as an androgen with a weak estrogen agonist compo-

TABLE 10.6 Progestins in the Medical Management of Endometriosis

Type	Dose	Duration of Therapy	Comments
Oral medroxyprogesterone acetate	10 mg tid, maximum of 100 mg/d	6 mo	Majority of patients report improved symptoms
Norethindrone acetate	5 mg QD and maximum dose 15 mg/d	6 mo	Pain reduction but not as great as that seen with GnRH agonists
Depot medroxyprogesterone acetate (DMPA)	150 mg IM every 12–14 wk		Efficacy similar to GnRH agonists and danazol
Subcutaneous medroxyprogesterone acetate	104 mg every 12–14 wk	Up to 18 mo	Pain reduction similar to that seen with GnRH agonists
Levonorgestrel-releasing intrauterine system (LNG-IUS)	52 mg levonorgestrel covered by silicone that releases 20 mcg/day for 5 yr	Up to 36 mo	Significant pain improvement
Etonogestrel subdermal implant	68 mg of etonogestrel, released over a 3-yr period	Up to 36 mo	Significant pain improvement

tid, three times daily; QD, daily; GnRH, gonadotropin-releasing hormone; IM, intramuscular.

nent. It has multiple mechanisms of action, including inhibition of pituitary gonadotropins, inhibition of ectopic endometrial growth, and inhibition of estrogen in the ovary.[56] It is given orally in divided doses from 400 to 800 mg daily, usually for 6 months. It is recommended for mild to moderate disease. When compared to placebo, danazol is effective in treating symptoms and diminishing lesions of endometriosis.[57] More than 80% of patients experience relief or improvement of symptoms within 2 months of treatment. A danazol-loaded intrauterine device was shown to improve symptoms of dysmenorrhea and dyspareunia with decreased systemic side effects.[58]

Side effects are reported in approximately 80% of users and include acne, male pattern hair growth, oily skin, and deepening of the voice, which may not be reversible.[59] Most of the side effects are dose dependent. Other anabolic and hypoestrogenemic effects include muscle cramps, decreased breast size, edema, weight gain, hot flashes, and mood swings. Danazol causes lipid abnormalities, including decreased HDL and increased LDL, which usually resolve about 3 months after discontinuation. Lipid and liver enzymes should be measured prior to beginning treatment. Danazol is contraindicated in liver disease and can elevate liver enzymes in other patients. Vaginal route administration of danazol is under investigation in the hopes of decreasing the systemic side effects while improving the endometriosis symptoms.[60]

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) agonists suppress pituitary gonadotropin secretion by triggering a downregulation of gonadotropin receptors, thus creating a low estrogen environment through decreased ovarian function. These medications are used for the treatment of moderate to severe pain associated with endometriosis, and in 70 to 90% of patients, there is adequate pain relief.[61] They also help reduce the progression of the disease. There is no evidence that they provide greater pain relief than OCPs or NSAIDs or that they are superior to OCPs as first-line therapy.[62]

GnRH agonists can be administered nasally (nafarelin acetate), intramuscularly (leuprolide acetate), or subcutaneously as an implant (goserelin acetate) (see Table 10.7 for recommended doses of GnRH agonists). The most commonly used is the depot injection which is usually administered every 1 to 3 months. Generally, initial treatment with a GnRH agonist is for 6 months. Treatment with GnRH agonists can be empirically instituted prior to laparoscopy diagnosis if endometriosis is clinically suspected, particularly if the patient has not responded to NSAIDs or OCPs and in whom other causes of chronic pelvic pain have been excluded. It is important to note that pain relief with GnRH agonists is not definitively diagnostic of endometriosis per se. If the GnRH agonist does not improve symptoms, further investigation of the pain is warranted.

TABLE 10.7 Recommended Doses for Gonadotropin-Releasing Hormone Agonists

Drug	Trade Name	Dose	Route of Administration
Goserelin acetate	Zoladex	3.6 mg every 28 d	Subcutaneous
Leuprolide acetate	Lupron	3.75 mg once per mo 11.25 mg every 3 mo	Intramuscular Intramuscular
Nafarelin acetate	Synarel	200 mcg twice a day	Intranasal

Use of GnRH agonists for women 18 years of age or younger is not recommended because of potential adverse long-term effects on bone formation and bone mineral density. Side effects of GnRH agonists are due to the hypogonadal, hypoestrogenic, or "medical menopause" state they induce. These include hot flashes, mood swings, vaginal dryness, insomnia, decreased libido, depression, headaches, lipid changes, and irregular vaginal bleeding. GnRH agonists also decrease trabecular bone density which increases the risk of osteoporosis, and for this reason treatment duration is limited and, in some instances, add-back regimens must be employed when GnRH agonists are used for longer durations (see Table 10.8 for add-back regimens used with GnRH therapy). Use of GnRH agonists for women 18 years of age or younger is not recommended because of potential adverse long-term effects on bone formation and bone mineral density. For treatments less than 6 months, the bone loss appears reversible.[63]

Although some clinicians use add-back therapy immediately upon the start of GnRH treatment, others use GnRH agonists when vasomotor symptoms occur during therapy. Use of a GnRH agonist for more than 1 year

TABLE 10.8 Endometriosis Add-Back Therapy

Drug	Dose
Norethindrone acetate (NETA)	5 mg QD
Conjugated equine estrogen (CEE) with NETA	0.625 mg CEE QD 5 mg NETA QD
CEE with medroxyprogesterone acetate	0.625 mg CEE QD 5 mg medroxyprogesterone acetate QD
CEE with medroxyprogesterone acetate	0.3 mg CEE QD 2.5 mg medroxyprogesterone acetate QD
Micronized estradiol	1 mg QD

QD, daily.

is not FDA approved, although there are reports about the use of a GnRH agonist with add-back therapy for up to 10 years with good pain relief and bone sparing.[64] Overall, the long-term effects of prolonged use of GnRH agonists even with add-back therapy are not known.[65,66] The use of add-back therapy has been shown to increase compliance.[67,68]

Common add-back regimens include progestins alone or combination estrogen and progestin. MPA alone for add-back, in the range of 10 to 30 mg per day has not proven effective; efficacy has been described for high doses of 100 mg/day, but this is a bit excessive.[68a] Norethindrone acetate alone at 5 mg per day is effective for eliminating hot flashes and is FDA approved for endometriosis add-back therapy.

Add-back regimens that include estrogen with progestin are effective in preventing significant bone loss and vasomotor symptoms.[69,70] Oral conjugated estrogens 0.625 mg daily with medroxyprogesterone acetate[70a] 5 mg daily have been shown to reduce hot flashes, preserve bone mineral density, but still maintain pain relief equitable with that experienced by patients on GnRH agonists alone. All patients using add-back regimens should still ensure they have adequate calcium intake (1000 mg daily). Once GnRH agonist treatment is stopped, it is reasonable to place the patient onto OCPs immediately (unless she is actively trying to get pregnant) or a progestin regimen, as described previously.

Aromatase Inhibitors

Aromatase inhibitors (AIs) inhibit the aromatase enzymes which convert the estrogen precursors testosterone and androstenedione to estradiol and estrone. They decrease estrogen production in the ovary and in other peripheral sources such as adipose tissue, and they also decrease local estrogen production in endometriotic implants. AIs have been reported to decrease the pain associated with endometriosis.[71-73] Letrozole (2.5 mg daily) and anastrozole (1 mg daily) are the most commonly used AIs for endometriosis.

AIs increase the production of follicle-stimulating hormone (FSH) with resultant ovarian stimulation and ovarian follicular development. It is recommended that if AIs are used to treat endometriosis, an oral contraceptive, GnRH analogue, or norethindrone acetate also be used to prevent ovarian stimulation. Use of these agents does not appear to decrease the effectiveness of AIs in treating the pain associated with endometriosis.[74] There is evidence that AIs in conjunction with a GnRH agonist lead to significantly better pain relief than use of GnRH agonists alone.[75,76] In one study, letrozole combined with norethindrone acetate (L+N) was more effective in reducing pain and deep dyspareunia than norethisterone acetate (NE) alone; however, the combination of the two also resulted in a higher incidence of adverse effects, cost more, and, similar to norethindrone acetate alone, pain symptoms recurred upon cessation of treatment. Patient satisfaction was similar for both L+N and N groups in the study.[77] More studies are needed, and currently, AIs are not considered definitive therapy for endometriosis.[33] These drugs are not FDA approved for use in endometriosis.

Other side effects of AIs include hot flashes, mood changes, muscle aches, breakthrough bleeding, headaches, and diarrhea. There are no large, randomized controlled trials on bone density in reproductive age women with AIs. Calcium and vitamin D are usually included in the regimen for bone health (see Table 10.9 for a summary of pros and cons of medical therapy in the treatment of endometriosis-associated pain).

TABLE 10.9 Medical Treatment for Pelvic Pain in Endometriosis

Advantages	Disadvantages
No risk of damaging pelvic organs as with surgery	Side effects of medications
No risk of adhesion formation as with surgery	High recurrence rates after discontinuation
Treats implants (may not see them with surgery)	Does not affect existing adhesions Does not affect endometriomas Ovulation suppressive treatments also prevent pregnancy No effect on fertility

Surgical Therapy

Surgery is indicated for definitive diagnosis, acute pain, endometriomas, and severe or incapacitating symptoms. Surgery is also indicated when expectant or medical management fails to improve symptoms or when patients refuse to use hormonal/nonsurgical treatments. Surgery is recommended with symptoms of advanced disease such as endometriomas, bowel, or urinary obstruction, or with anatomic distortion of the pelvic organs[6] (see Table 10.10 for surgical indications for endometriosis). Surgery is usually classified as conservative or definitive.

TABLE 10.10 Indications for Surgical Management of Endometriosis

- Pain that is severe, incapacitating, and significantly impairs functionality
- Severe and advanced disease that has resulted in significant distortion of anatomy, impairment of organs, or endometriomas
- Failure of expectant or medical management approaches
- Lack of adherence or intolerance to medical therapies
- Endometriosis emergencies
  - Ruptured endometriomas
  - Torsion of endometriomas
  - Obstructive uropathy
  - Bowel obstruction

Conservative Surgery

Conservative surgery preserves the uterus and as much of the female pelvic organs as possible, especially the ovaries. Conservative surgery can be conducted through laparoscopy or laparotomy. Laparoscopy has advantages of faster recovery, better visualization, and less trauma. The goal of conservative surgery is to restore the normal pelvic anatomy. This can be accomplished through lysis of adhesions, removal of endometrial implants by sharp excision, fulguration (monopolar or bipolar cautery), or laser ablation. No randomized trial has compared implant removal methods, for example, electrosurgical, laser, ultrasonic, or robotic, and their different success rates.

When undertaking surgery for endometriosis, consider scheduling the surgery in the follicular phase to prevent disruption/resection of a corpus luteum, which can be confused with an endometrioma. Patients for diagnostic laparoscopy should be consented for surgical treatment at time of diagnosis. Atraumatic graspers; fine sutures; and absorbable, oxidized, regenerated, cellulose barriers should be used to decrease associated adhesion formation postoperatively.[78]

A prospective, randomized, double-blind, controlled trial reported no differences in pain scores at diagnostic laparoscopy versus laser laparoscopy at 3 months, but there was a significant decrease in pain in the laser-treated group at 6 months after the placebo effect had abated.[79] In other studies, 80% of patients who had operative laparoscopy had symptom improvement at 6 months compared to 32% in an expectant management group.[80,81] There are no current studies specifically investigating the stage of disease and corresponding surgical response. The risk of reoperation has been estimated at about 20% of patients in 2 years and close to or slightly above 50% at 5 and 7 years, respectively.[82,83] The only variable that correlated with the need for reoperation in one study was the age of the patient at the time of the original surgery, with younger patients having a higher probability of repeat surgery.[82]

Studies have also investigated presacral neurectomy and laparoscopic uterosacral nerve ablation (LUNA) for pain relief. Presacral neurectomy, which decreases sympathetic innervations of the uterus through the superior hypogastric plexus, may have benefit in treatment of midline endometriosis-associated pain.[84] One randomized controlled trial of 71 women with presacral neurectomy at conservative surgery showed decreased midline pain but no difference in other symptoms.[85] Presacral neurectomy is associated with possible postoperative side effects of urinary dysfunction or constipation, so patients should be counseled accordingly.

The concept behind LUNA is that it will disrupt the efferent nerve fibers in the uterosacral ligaments and result in decreased uterine pain. However, studies have not demonstrated efficacy in this procedure, and a recent Cochrane Review concluded there is insufficient evidence to recommend the use of nerve interruption in the management of dysmenorrhea.[86,87]

Definitive Surgery

Definitive surgery involves the removal of the uterus with possible removal of the ovaries and fallopian tubes if necessary. Definitive surgery is only indicated when future fertility is not desired and symptoms of severe endometriosis are incapacitating, intractable pain despite persistent medical treatment and conservative surgery, multiple previous conservative surgeries, or with coexisting pelvic pathology, which requires hysterectomy. The decision to remove the ovaries is based on age, proximity to menopause, and the severity of endometriosis and/or existing lesions on the ovaries. If no disease is present on the ovaries, bilateral oophorectomy is usually avoided in younger reproductive age women to avoid menopausal symptoms and preserve bone health. Women younger than age 30 years who undergo definitive surgery for endometriosis report more residual symptoms and overall disruption in their life compared to older women.[88]

In a study comparing recurrent symptoms 7.8 to 11 years after hysterectomy with and without oophorectomy for endometriosis, most patients did not require repeat surgery, even when their ovaries were conserved. The need for repeat surgery at 2, 5, and 7 years for women who had their ovaries removed was 96, 92, and 92%, respectively, whereas for those who conserved their ovaries, it was 96, 87, and 77%, respectively.[89]

Symptoms of endometriosis may recur in up to 15% of women after removal of their ovaries, whether they took estrogen therapy postoperatively or not. In patients undergoing surgery for recurrent endometriosis after definitive pelvic surgery, the most common sites of lesions are the large and small bowel. These likely represent lesions that were not excised at the time of surgery and are actually persistent disease, not truly recurrent disease.

If a woman undergoes definitive surgery and has her ovaries removed, hormonal therapy (HT) with an estrogen and possibly, a progestin should be considered.[33] There is no apparent benefit to delay in the initiation of hormone therapy postoperatively in terms of recurrence rate. Based on concerns that unopposed estrogen therapy only may induce malignant transformation in any residual endometrial implants, some practitioners use both estrogen and progestin therapy postoperatively.[16] However, there is no outcome-based evidence that supports this practice.

Combination Therapy

Medical Therapy Before Surgery

Proponents of preoperative medical therapy before surgery for pelvic pain suggest it decreases the size of the

endometriotic implants and vascularity of the pelvis and the amount of surgical dissection needed. However, there is no evidence that preoperative HT prolongs pain relief, increases future pregnancy rates, or decreases recurrence rates, although it may reduce the size of implants and the extent of the surgery required.[90,91]

Medical Therapy After Surgery

Medical therapy after surgery for pelvic pain is proposed to treat incomplete removal of implants, residual microscopic disease, lengthen pain-free interval, and decrease recurrence. There is evidence that placement of the levonorgestrel-releasing intrauterine device postoperatively decreases symptomatic recurrence when compared to controls (including GnRH) for postoperative therapy.[92,93] Other studies support postoperative GnRH agonists to decrease recurrence rates, but no benefit was noted for the outcomes of pain, patient satisfaction long-term, or pregnancy rates.[91]

Investigational Therapies

Other treatment modalities are currently being investigated for treatment of pain associated with endometriosis. Infliximab, anti–tumor necrosis factor (TNF) alpha, is invested in the inflammation pathway treatment of endometriosis.[94] Pentoxifylline is another immunomodulator drug being studied, but it has no benefit for fertility.[95] Angiogenesis promoters and matrix metalloproteases are more drug targets.[96] Mifepristone (RU-486), a progesterone antagonist, has been studied in small, nonrandomized trials and does decrease pain symptoms and induce regression of lesions.[97] Selective progesterone receptor modulators are a newer class of medications being investigated for treatment of endometriosis.[98] Gestrinone is an antiprogesterone steroid used for treatment of endometriosis available in Europe but not in the United States.[99] In the homeopathic realm, acupuncture and Chinese herbal medicine have been recommended but not clinically supported.[100,101]

Clinical Approach

Endometriosis-associated pelvic pain can be treated with different medical or surgical modalities. The most important clinical step is making the diagnosis. Diagnostic laparoscopy with plans for operative ablation or resection of any lesions found at the time is recommended when the diagnosis is questionable. For minimal or mild symptoms of endometriosis, empiric NSAIDs and continuous OCPs are good options. If this fails and the clinical suspicion of endometriosis is high, other treatment modalities such as progestins or GnRH agonists can be tried. At any time, if the diagnosis is questionable or medical treatment fails, then diagnostic laparoscopy that includes treatment of any lesions encountered should be considered. For women with severe symptoms who have completed childbearing, consider definitive surgery. Endometriomas do not respond to medical therapy and should be removed surgically if symptomatic.

Surgical Treatment of Endometrioma(s) or Deep Endometriosis

Endometriomas, often referred to as chocolate cysts, contain blood, fluid, and endometrial tissue. They are thought to result from the progressive invagination of endometriotic lesions on the ovarian cortex that ultimately form cystic structures. Endometriomas usually present with chronic pain symptoms. It is estimated that 50% of women with endometriosis develop endometriomas, and they are often bilateral.[102] The diagnosis is usually made by pelvic exam and ultrasound demonstrating a thick-walled cystic mass that may be unilocular or multilocular with homogeneous, hypoechoic "carpet" of low-level echoes.[103] When the ultrasound is suggestive of endometriomas, there is a strong likelihood that moderate to severe endometriosis is present.[104]

Surgery is the preferred therapy because medical treatment, even with GnRH agonists, is unlikely to resolve it. Some recommend removal if the cyst is more than 3 cm.[105] Surgery also provides the benefit of histologic confirmation so other less likely diagnoses of malignancy or borderline tumors can be excluded.[106,107] Endometriosis of the ovary is associated with a small increase in the risk of ovarian cancer; the most common histologic types are clear cell and endometrioid.

Laparoscopic excision has been shown to be superior to laparotomy with regards to analgesia requirements and recovery. Because they are almost always firmly attached to the ovary and its normal cortex where oocytes are embedded, ovarian reserve may be diminished after excision.[108] Simple drainage, even with coagulation of the cyst wall, is associated with a high recurrence rate (up to 88% at 6 months follow-up) and is not recommended. Laparoscopic excisional cystectomy is superior to drainage and coagulation of cyst bed in terms of decreased symptoms, increased symptom-free interval, and improved pregnancy rate.[109] It is better to create a circular incision over the endometrioma and then strip it from the ovary than simply try to strip or peel it off the wall because the former technique reduces the number of ovarian follicles removed with the specimen. On the inner cyst wall, endometriosis rarely penetrates more than 1.5 mm into the cyst capsule so deep dissection is not necessary.[110] Any physiologic cysts noted at the time of surgery (follicular cysts or hemorrhagic corpus luteum cysts) should be left alone in order to retain as much normal ovarian tissue as possible.

Endometrioma recurrence after surgery is 20 to 30% in 2 to 5 years, and further surgery needs to be evaluated on an individual basis, given the risk of

further reduction or complete loss of ovarian function with repeat excision(s).[111,112] Pregnancy and lactation after surgical therapy for endometriosis appears to reduce the risk of recurrence. Oophorectomy is less likely to result in recurrence than cystectomy and is a reasonable option for women who have completed childbearing. Patients should be counseled that it is still possible that a retained retroperitoneal ovarian remnant may result in a recurrent adnexal mass. Long-term cyclic and continuous OCPs postoperatively have been shown to reduce and delay endometrioma recurrence.[113]

Endometriosis may also present as deeply infiltrating peritoneal disease, which usually involves the uterosacral ligaments, rectovaginal septum, bladder, ureters, or bowel. Medical therapy of deep endometriosis with significant symptoms is not very effective, and surgical resection is usually necessary. However, there is some data that hormonal treatment of rectovaginal endometriosis for 6 to 12 months significantly decreases dysmenorrhea, dyspareunia, and dyschezia, although recurrence rates are quite high once the therapy is discontinued.[114] Bowel involvement is difficult, and in certain cases, the therapeutic option is bowel resection.[115] There is no consensus on the type or extent of resection necessary. Surgical resection does not improve future fertility rates. Hysterectomy and bilateral oophorectomy without resection of deep infiltrating endometriosis is inadequate treatment and will not obviate symptoms. Even after surgical treatment for deep endometriosis, recurrence rates are high, and medical treatment rather than repeat surgery may be useful.[116]

ENDOMETRIOSIS-ASSOCIATED INFERTILITY

Infertility is usually defined as no conception after a year of regular, unprotected intercourse. The normal monthly fecundity rate, the probability of a woman achieving a live birth, is 15 to 20% and decreases with age. Monthly fecundity range from 2 to 10% in infertile women with endometriosis.[117] Endometriosis is a very prevalent diagnosis in patients with infertility. In women diagnosed with endometriosis, about 30 to 50% are infertile, and early studies suggest that 25 to 50% of infertile women have endometriosis.[118,119] There is no evidence that endometriosis is associated with recurrent pregnancy loss.[120] A full infertility evaluation should be completed prior to starting therapy for women with endometriosis and infertility.

There appears to be a relationship between infertility and endometriosis, but the specific mechanisms have not been clarified and likely depend on the stage of disease.[103] Proposed mechanisms for the links between infertility and endometriosis altered peritoneal function, abnormal endometrial function, abnormal fertilization and implantation, altered systemic immune function, and endocrine and ovulatory abnormalities.[121]

There is no conclusive evidence that stage I or II endometriosis is a cause of infertility, although it is possible that the inflammatory processes associated with endometriosis may impair ovarian, peritoneal, tubal, and endometrial function.[122] Changes in the peritoneal fluid may inhibit sperm function or ciliary function.[123,124]

Severe cases of endometriosis are often associated with severe adhesive disease, and this may impair fertility by interfering with tubo-ovarian motility and ultimately, with the pick-up function of the fimbrial end of the tube. Major adhesions may also impair oocyte release or block sperm entry into the peritoneal cavity. It has also been suggested that decreased fertility in advanced endometriosis may result from a premature depletion of the ovarian follicle pool, abnormal folliculogenesis, or a reduced fertilization potential of oocytes.

Treatment of Infertility

When considering infertility treatment associated with endometriosis, multiple factors should be considered. Women older than age 35 years should be treated more aggressively due to their already declining fecundity. The optimal therapy for endometriosis-associated infertility remains controversial. Therapies to consider include expectant management, medical, surgical, or assisted reproductive technologies (see Fig. 10.6 for an algorithm of the management of endometriosis-associated pain and infertility).

Counseling patients on fertility outcomes and determining which fertility treatment to start can be daunting. Adamson and Pasta[125,126] have developed a clinical tool, the endometriosis fertility index (EFI), for infertile patients with endometriosis to predict the probability of pregnancy after surgical staging of endometriosis followed by fertility treatment excluding in vitro fertilization (IVF). The EFI was derived from patients with all stages of endometriosis. The EFI combines historical and surgical information from the patient, which creates a sum of factors from 0 to 10. Historical factors are based on age and length of infertility, and the surgical factors are a combination of the developed "least function" (LF) score and American Fertility Society (AFS), now the American Society for Reproductive Medicine (ASRM), endometriosis surgical staging score. The LF score is created intraoperatively from information about the function of the tubes, fimbriae, and ovaries. The percentage of pregnancies achieved increases with increasing EFI over time (see Fig. 10.7). Hence, an EFI of 0 represents the poorest fertility prognosis and 10 the best prognosis. The EFI can be used to aid in predicting pregnancy rates of patients with infertility associated with endometriosis and used to further guide their counseling[125,126] (see Table 10.11 for the EFI scoring system and Fig. 10.7 for the pregnancy percentages over time according to EFI scores).

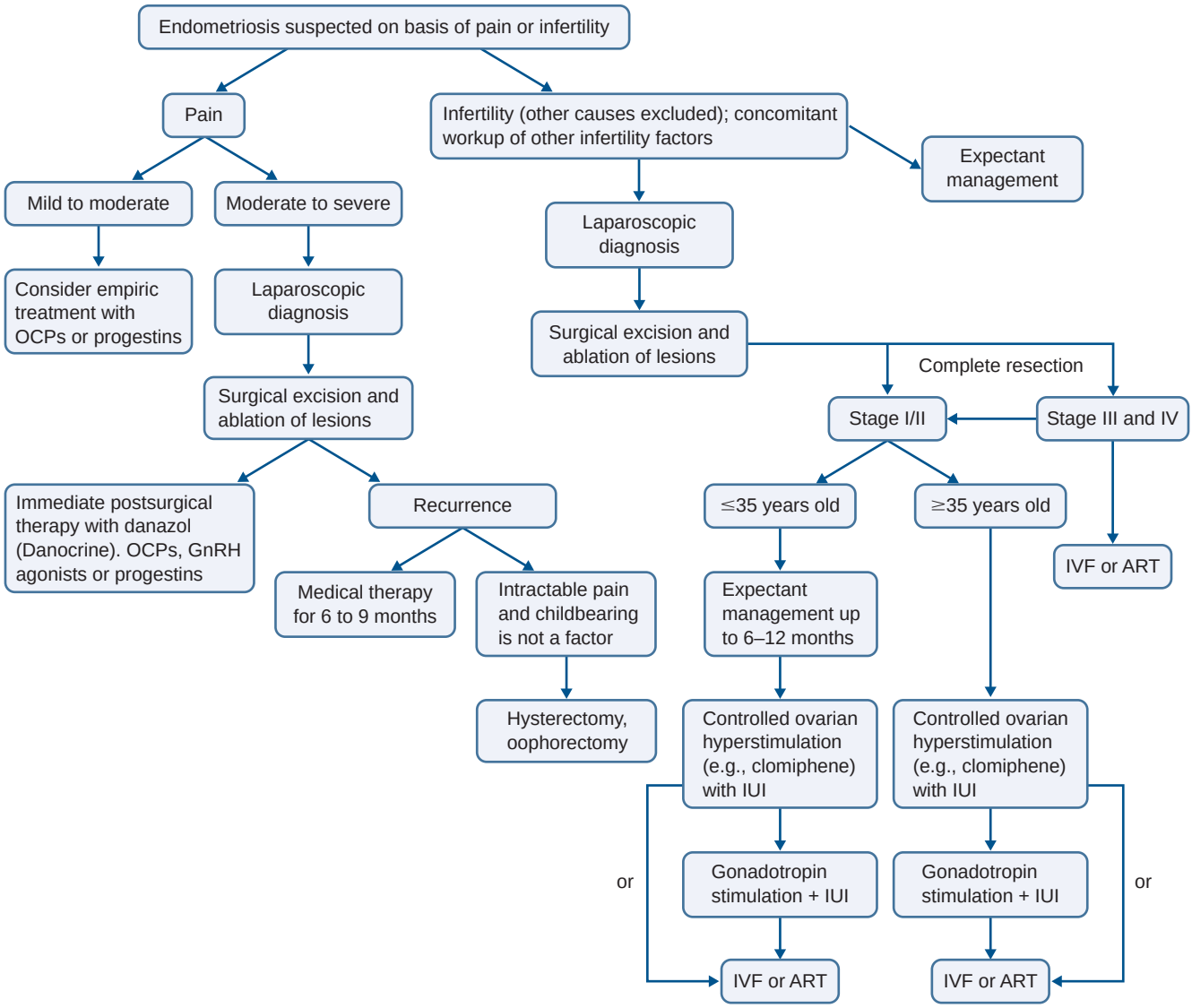


FIGURE 10.6 Algorithm for managing pain and infertility associated with endometriosis. OCPs, oral contraceptive pills; GnRH, gonadotropin-releasing hormone; IUI, intrauterine insemination; IVF, in vitro fertilization.

Expectant Management

Expectant management is a reasonable option for some younger patients. Despite impaired fertility, women with minimal to mild disease without severe adhesions are able to conceive spontaneously. Women with minimal disease without treatment after 5 years have a cumulative pregnancy rate of about 90%.[127] In a retrospective review, expectant management was compared to conservative surgery. In the study, 16 patients were managed expectantly with a 75% pregnancy rate in 1 year, which was similar to the 29 patients after conservative surgery with a 72% 1-year pregnancy rate.[128] Another study found a cumulative pregnancy rate of 55% at 18 months with expectant management.[129] However, if any laparoscopy is to be performed for diagnosis, operative laparoscopy should be considered based on studies that suggest an increase in pregnancy rates follow laparoscopic surgery.[130,131]

Medical Therapy

Medical therapy is effective in treating endometriosis-associated pelvic pain, but it is ineffective when treating infertility. There is no evidence that any medical treatment alone improves fecundity in women with endometriosis and infertility. Use of medical treatment will only delay fertility, may be detrimental to fecundity, and in some cases, carry significant costs and/or side effects. Many studies illustrate that no treatment or surgical treatment is superior to medical treatment alone for endometriosis-associated infertility.[132] Danazol, GnRH agonists, and progestins do not increase fertility in minimal to mild endometriosis.[130,132]

TABLE 10.11 Endometriosis Fertility Index

Historical Factors		Surgical Factors	
Points	**Description**	**Points**	**Description**
2	If age is ≤35 years	3	If LF score = 7–8 (high score)
1	If age is 36–39 years	2	If LF score = 4–6 (moderate score)
0	If age is ≥40 years	0	If LF score = 1–3 (low score)
2	If years infertile is ≤3	1	If AFS endometriosis lesion score <16
0	If years infertile is >3	0	If AFS endometriosis lesion score ≥16
1	If there is a history of prior pregnancy	1	If AFS total score <71
0	If there is no history of prior pregnancy	0	If AFS total score ≥71

The endometriosis fertility index (EFI) derived by Adamson and Pasta.[125,126] Historical factors are based on age and length of infertility, and the surgical factors are a combination of the developed "least function" (LF) score and American Fertility Society (AFS), now the ASRM, endometriosis surgical staging score. From Adamson GD, Pasta DJ. Pregnancy rates can be predicted by validates endometriosis fertility index (EFI). *Fertil Steril.* 2002;77(suppl 2):s48.

Surgical Therapy

Surgical therapy alone may increase fertility in patients with endometriosis-associated infertility, although its value in minimal to mild endometriosis is controversial. One meta-analysis found that surgery was of significant benefit, but the degree of benefit appears to be small: The number of women who must have surgery to garner an additional pregnancy is approximately eight.[133] Another analysis noted that 12 additional women would have to undergo surgery to achieve one additional pregnancy.[134] There are two randomized controlled trials on patients with minimal to mild endometriosis investigating surgery and pregnancy rates, which differed in time frames, inclusion criteria, and study power.[131,134]

Although there are no randomized fertility trials for surgical treatment in stage III or IV endometriosis, a nonrandomized study of moderate to severe endometriosis reported significantly increased pregnancy rates after surgery.[121] The reported pregnancy rate after surgery for advanced endometriosis is 40 to 50%.[135] If pregnancy does not result after the initial surgery, subsequent surgeries are unlikely to be effective for increasing fecundity, and ART should be considered. There is some evidence that the removal of deeply infiltrating endometriosis may improve IVF outcomes, although these were not randomized controlled trials.[136,137]

Combination Medical and Surgical Therapy

Medical and surgical therapies are often combined in the treatment of advanced endometriosis. However, there are no randomized controlled trials with preoperative medical treatment and fertility outcomes. A Cochrane Review found that preoperative hormonal suppression reduced the extent of surgery required, but in the absence of convincing evidence of increased pregnancy outcomes, the possible benefits must be considered against the increased costs and potential morbidities.[91] Overall, according to the same Cochrane Review, postoperative medical therapy after conservative surgery for endometriosis does not show significantly increased pregnancy rates.[91]

Superovulation, Insemination, and Assisted Reproductive Techniques

Infertility may be improved by multiple techniques including intrauterine insemination (IUI), controlled ovarian hyperstimulation, and assisted reproductive techniques such as IVF. There have been few randomized controlled trials on infertility treatment for different stages of endometriosis. Several randomized trials have found that ovulation induction, with or without IUI, increases fertility rates in endometriosis-associated infertility where there is no distorted pelvic anatomy or male factor infertility.[138,139] There is evidence that the use of both gonadotropin agents and IUI may have the highest monthly fecundity rates.[140] Ovarian stimulation, however, may lead to the progression of endometriosis, so controlled ovarian hyperstimulation with IUI should probably be limited to a maximum of three to four cycles.[141]

The effect of endometriosis on IVF outcomes is not certain. Some studies demonstrate success rates that are comparable to those of unexplained or tubal factor infertility, and others find reduced success rates.[142–145] However, the probability of achieving a pregnancy by IVF is still acceptable with endometriosis.[146]

In patients with moderate to severe endometriosis, 6 months of GnRH analog hormonal suppression appears to increase pregnancy rates.[147]

Clinical Approach

Therapy for women with endometriosis and infertility begins with the entire infertility evaluation including semen analysis and assessment of tubal patency. Unfortunately, there are few randomized controlled trials to guide evidence-based clinical decision making. In women with minimal or mild endometriosis, the first decision is whether to perform laparoscopy prior to initiating treatment. In support of laparoscopy, the larger randomized controlled trial reported increased fecundity following laparoscopic surgery. If the patient also has pain, then laparoscopy should be considered. If the patient is older than age 35 years or has advanced stage endometriosis, then more aggressive treatment should be pursued. Expectant management is an option in younger patients. A stepwise approach of controlled ovarian stimulation, IUI, and advanced assisted reproduction techniques is quite reasonable.

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description		Left	Right		
4	=	Normal	Fallopian Tube				
3	=	Mild Dysfunction					
2	=	Moderate Dysfunction	Fimbria				
1	=	Severe Dysfunction					
0	=	Absent or Nonfunctional	Ovary				
			Lowest Score		+		=
				Left		Right	LF Score

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: [ ] Historical + [ ] Surgical = [ ] EFI Score

ESTIMATED PERCENT PREGNANT BY EFI SCORE

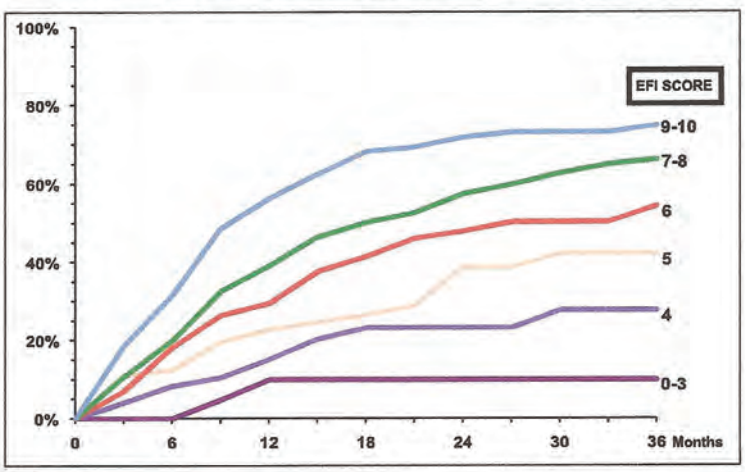


FIGURE 10.7 Pregnancy percentage over time according to EFI score. (From Adamson GD, Pasta DJ. Pregnancy rates can be predicted by validated endometriosis fertility index [EFI]. *Fertil Steril*. 2002;77[suppl 1]:s48.)

CLINICAL NOTES

- The estimated prevalence of endometriosis is 6 to 10% of reproductive age women in all ethnic and social groups.
- When a first-degree relative is affected, a woman has 7% increased chance of having endometriosis.
- Endometriosis is commonly found in the ovaries, anterior and posterior cul de sac, and broad ligaments. It can be found in many other places less commonly including the bowel and bladder.
- Symptoms include secondary dysmenorrhea, dyspareunia, dyschezia, dysuria, noncyclic pelvic pain, abdominal cramps, and back pain. Most women do not have all of the symptoms. Infertility is a common presenting complaint.
- The most common physical findings are tenderness of the posterior cul de sac or nodularity of the uterosacral ligaments.
- The American Society for Reproductive Medicine has a commonly used staging system for endometriosis classified into minimal, mild, moderate, and severe. The extent of disease does not always correlate with clinical symptoms.
- Definitive diagnosis of endometriosis requires direct visualization of the lesions by laparoscopy or laparotomy. Removal of lesions at time of diagnosis is preferable.
- Other causes of pain need to be investigated when considering the diagnosis of endometriosis.
- The treatment of endometriosis depends on the severity of symptoms, extent of disease, location of disease, age of patient, and desires for future fertility.
- NSAIDs are affordable, available, and tolerable. They are a good first-line treatment, especially combined with an OCP, for treatment of minimal or mild endometriosis.
- OCPs can be taken continuously or cyclically for minimal or mild endometriotic symptoms.
- Multiple formulations of progestins exist. Progestins are an effective treatment for pain associated with endometriosis with 90% of women achieving complete or partial relief. Recurrence of symptoms is high after treatment is stopped.
- Danazol improves more than 80% of symptoms in 2 months, but its significant side effect profile limits its use. Lipid and liver enzymes should be monitored prior to use. Deepening of the voice may be a nonreversible side effect. Other routes of administration are currently being investigated.
- GnRH agonists are an appropriate treatment for endometriosis-associated pain, but they are relatively expensive and induce a "medical menopause." Add-back therapy should be considered for bone health.
- AIs are currently being investigated. They are usually prescribed with an OCP or GnRH analog, along with calcium and vitamin D supplementation.
- Conservative therapy for endometriosis pain is effective but at 5 years has an estimated risk of recurrence of 19%.
- Definitive surgery should only be considered if childbearing is complete. Oophorectomy is done based on ovary involvement and patient's age. If oophorectomy is completed, hormonal replacement with estrogen and/or progesterone should be considered.
- Endometriomas should be removed surgically.
- Monthly fecundity rates are lower in patients with endometriosis.
- Medical therapy, excluding controlled ovarian hyperstimulation, is not effective in treating infertility associated with endometriosis.
- Surgery may be useful in improving fecundity in endometriosis-associated infertility, especially in the advance stages of endometriosis.
- If the patient is older than age 35 years or has advanced stage endometriosis, more aggressive infertility treatment should be pursued.
- For minimal to mild endometriosis-associated infertility, beginning the treatment with timed cycles or expectant management is appropriate in younger patients.
- Empiric clomiphene treatment with or without IUI or gonadotropin treatment with or without IUI are an appropriate initial treatments for endometriosis-associated infertility. IVF improved fecundity in patients with endometriosis-associated infertility but is usually not first-line treatment.

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CHAPTER 11

Infertility and Recurrent Pregnancy Loss

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INFERTILITY

Infertility is defined as the inability to conceive after 12 or more months of regular intercourse without contraception.[1] Infertility is common—approximately 10% of couples have difficulty conceiving a child—and has important psychological, economic, demographic, and medical implications.[2] Major advances in assisted reproductive treatment technologies have occurred over the last few decades. However, an accurate assessment of factors affecting the fertility of both partners is the initial step to provide targeted treatment. The elements of a standard infertility evaluation are evolving as the available evidence base for commonly performed diagnostic procedures and tests is being reviewed.

Over the last few decades, societal factors affected rates of infertility related to aging in women.

In the United States, there have been increases in the mean maternal age at first birth (25.1 years in 2002 versus 21.4 years in 1968) and in the mean age of women delivering a child (27.3 years in 2002 versus 24.9 years in 1968).[3] In part, this trend may be explained by an increasing emphasis on career and educational goals. In addition, a later mean age at first marriage has been observed in countries like England and the United States.[4] The advent of widely accessible methods of birth control may also be contributing to a delay in childbirth by allowing earlier unplanned pregnancies to be avoided. With the increased availability of services and improved diagnostic and therapeutic management, more couples are now able to access infertility services.

EPIDEMIOLOGY (OF INFERTILITY)

A couple is said to be infertile if they have been trying to achieve a pregnancy for more than 1 year without success.[1] The roots for this somewhat arbitrary definition lie in a study from 1956 analyzing a cohort of 5574 English and American women engaging in unprotected intercourse who ultimately conceived over a 10-year period.[5] In this study, 50% conceived within 3 months, 72% within 6 months, and 85% within 12 months.

The definition can also be justified from a statistical perspective using the concepts of fecundity and cumulative pregnancy rates.

Fecundity (f) represents the probability of conception per month of effort and is calculated by dividing the number of conceptions (C) by the person-months of exposure (T).

$$f = C/T$$

It must be remembered that even in infertile populations, fecundity is almost never zero, and for fertile couples, it is approximately 0.20. Assuming a 20% monthly probability of pregnancy among normally fertile couples, the cumulative probability of pregnancy after 12 months is 93%.[6] Therefore, there is a 7% statistical probability that a normally fertile couple does not conceive after 12 months, close to the 5% statistical threshold for a type I error (in this case, a false rejection of the null hypothesis of normal fertility). The 1-year definition of infertility is thus both statistically and clinically meaningful. Therefore, it is reasonable to perform a full infertility evaluation only when a couple has attempted 12 months of unprotected intercourse. With increasing age, however, it is common practice to not delay the workup given the rapid decrease in ovarian reserve. Therefore, many specialists recommend testing for common causes of infertility after 6 months in a couple with a female older than age 35 years and immediately in a couple with female older than age 40 years .[7]

Infertility can be considered as a reduction in fecundity to less than that of the general population, and the evaluation is designed to identify factors that are responsible for diminished fecundity. Based on a woman's history, infertility is classified into two categories: primary and secondary. Primary infertility implies no antecedent pregnancy, and secondary infertility is defined by a history of any pregnancy, including abortions and ectopic pregnancies.

Estimating the prevalence of infertility is difficult because of inconsistent definitions in epidemiologic reports. Between 1965 and 1988, the prevalence appeared to remain stable at approximately 13% of American women aged 15 to 44 years (excluding surgically sterilized individuals).[8,9] Although the prevalence of infertility has remained at approximately 13 to 15% of the U.S.

population since the mid-1980s, more couples are seeking medical and surgical services for impaired fecundity. The number of childless women who are 35 to 44 years old increased by more than 1 million from 1982 to 1988. Women were 2 to 3 years older in 1990 than in 1979 when they delivered their first child, and significantly, more women never had a child.[10]

Differences in the distribution of primary and secondary infertility have a direct impact on the use of fertility services because women with primary infertility are more likely to use medical services than women with secondary infertility. Overall, about half of all infertile couples will seek treatment, although only 25% will obtain assistance from an infertility specialist.[11] Geographic variations in the use of infertility services are in part mediated by differences in state-mandated insurance coverage of assisted reproductive services.[12] Approximately half of couples with infertility eventually conceive. Likelihood of conception is influenced by several factors, including the duration of infertility, the causes of infertility, and the age of the woman at the time of treatment.

In a World Health Organization (WHO) study of 8500 infertile couples, the distribution of medical conditions contributing to infertility was analyzed.[13] In developed countries, female factor infertility was reported in 37% of infertile couples, male factor infertility in 8%, and both male and female factor infertility in 35%. Five percent of couples had unexplained infertility and 15% became pregnant during the study. This study illustrates the importance of evaluating both partners of the infertile couple, focusing on the major processes which affect fertility.

INVESTIGATION OF THE INFERTILE COUPLE

Clinical evaluation of the infertile couple is customarily initiated if a pregnancy has not occurred after 1 year of regular unprotected intercourse. Earlier assessment is warranted in women who have a history of oligomenorrhea/amenorrhea, are older than age 35 years, and have known or suspected pelvic pathology.[14] Initially, a thorough history and physical exam are essential to guide the initial individual diagnostic approach. The history should include details on patient age, the duration of infertility, results of any previous evaluations, and a menstrual history to help determine ovulatory status.[15] A sexual history, including sexual dysfunction and frequency of coitus, should be obtained, as well as a complete medical, surgical, gynecologic, and obstetric history. A personal and lifestyle history is essential, given that factors such as occupation, exercise, stress, dieting, smoking, as well as drug and alcohol use, can affect fertility. For example, smoking or other tobacco use, marijuana, and cocaine may reduce fecundity in men and women.[16] Occupational and environmental exposures associated with decreased fecundity are reviewed in a separate chapter. Some centers find it helpful to distribute a detailed questionnaire to patients before their first visit to obtain information that is sometimes difficult to express in an office interview. Such a questionnaire is available from the American College of Obstetricians and Gynecologists (ACOG) or the American Society for Reproductive Medicine (ASRM).

The physical exam may identify potential causes of infertility and previously undiagnosed health conditions. For example, a goiter may be palpated in a patient with underlying thyroid disease, and male pattern baldness may be found in a female patient with androgen excess. The pelvic exam may reveal tenderness or masses in the adnexa or posterior cul de sac, suggesting endometriosis.

After the initial evaluation, further diagnostic assessment can be planned. As part of preconception evaluation and counseling, a rubella titer should be ordered, indicated immunizations should be administered, HIV testing, and cystic fibrosis (CF) carrier testing should be offered to all couples. Prenatal vitamins containing adequate amounts of folic acid should also be prescribed at this time to decrease the risk of fetal neural tube defects.[17] Serum thyroid-stimulating hormone (TSH) testing is performed because undiagnosed maternal hypothyroidism is associated not only with anovulatory infertility but also with adverse fetal neuropsychological development.[18]

A key objective of further testing is to rule out male factor infertility, anovulation, or tubal obstruction[7] (see Table 11.1). Most couples will require semen analysis, an assessment of ovulatory function, an assessment of the uterine cavity, and an assessment of tubal patency by hysterosalpingography or laparoscopy. Ovarian reserve testing by estimation of follicle-stimulating hormone (FSH) and estradiol on cycle day 3 is often ordered as part of the initial testing. Laparoscopy may be considered in a minority of cases when endometriosis, intrapelvic adhesions, or fallopian tube disease is suspected.

Expert committees may offer guidance in the initial evaluation of the infertile couple such as the ASRM Practice Committee (www.asrm.org).[19]

TABLE 11.1 Assessment of Infertility

Initial tests for couples with infertility:

- Semen analysis (to assess any male factor component)
- Menstrual history, assessment of LH surge in urine prior to ovulation, and/or luteal phase progesterone level (to evaluate ovulatory function)
- Hysterosalpingography (to determine tubal patency and the status of the uterine cavity)
- Day 3 serum FSH and estradiol levels (to evaluate ovarian reserve)

In some instances, the following additional tests may be indicated:

- Pelvic ultrasound (to look for uterine myomas and ovarian cysts)
- Laparoscopy (to determine if there is endometriosis or other pelvic pathology)
- Further assessment of ovarian reserve in women older than age 35 years; this may involve a clomiphene citrate challenge test, ultrasound for early follicular antral follicle count, day 3 serum inhibin B level, or anti-Müllerian hormone measurement
- Thyroid function testing

LH, luteinizing hormone; FSH, follicle-stimulating hormone.

ANOVULATORY INFERTILITY

Ovulatory dysfunction and anovulation affect 15 to 25% of all infertile couples seeking therapy. The ultimate proof of normal ovulation is a subsequent pregnancy, but several other pieces of evidence can be used to confirm the presence or absence of normal ovulation. The process leading to ovulation is composed of several components; disruption of any of these can impede ovulation or the capacity of a mature oocyte to fertilize. Treatment of ovulation disorders remains one of the most successful of all infertility treatments.

Evaluation of Ovulatory Function

History

The first and arguably most telling piece of information about ovulatory function is a thorough menstrual history. Generally speaking, regular menstrual cycles between 28 and 35 days are ovulatory. Shorter or longer cycles may signify anovulation; in shorter cycles, this may be representative of a shortened follicular phase seen in aging, and longer cycles may belie an inadequate luteal phase resulting in an endometrium unreceptive to an embryo. A patient who reliably reports very regular 28-day menstrual cycles is unlikely to have anovulation. On the other hand, a woman who reports infrequent, irregular menses and no moliminal symptoms (or who gives an unclear history of her menstrual cycles) is likely oligo- or anovulatory and should be evaluated.

Background: Physiology of Normal Ovulation

A review of the normal hormonal events that regulate the ovulatory process is essential to an understanding of the tests devised for ovulation detection. The trophic effects of both FSH and luteinizing hormone (LH) result in maturation of ovarian follicles. Release of both FSH and LH from the anterior pituitary is controlled by gonadotropin-releasing hormone (GnRH), which is produced in the hypothalamus in a pulsatile fashion. The ovulatory process is characterized by a rapid midcycle rise in LH that culminates in the LH peak. A consensus from previous reports places the onset of the serum LH surge approximately 36 to 38 hours before ovulation.[20] FSH also increases midcycle but to a lesser degree than LH. The luteal phase is characterized by a rise in the concentration of progesterone produced by the corpus luteum, with maximal concentration reached about 8 days after the LH peak. The menstrual cycle length is variable, with the variation residing in the follicular phase. The length of the luteal phase is consistently 14 days.

Midluteal Serum Progesterone Testing

Detection of serum progesterone greater than 3 ng/mL on day 21 suggests the presence of a functioning corpus luteum, indicating that ovulation occurred.[21] One report indicated that midluteal progesterone levels greater than 8.8 ng/mL were present in more than 95% of spontaneous conception cycles.[22] Given the large variability in progesterone secretion throughout the luteal phase in normal patients, it is controversial whether a higher level of progesterone indicates a "better" ovulation than a lower level.

Urinary Luteinizing Hormone Testing

Detection of an LH surge, suggesting that ovulation is imminent, allows the patient to appropriately time intercourse.[23] There is a 4- to 6-hour lag between serum and urinary LH surges. More than 90% of ovulation episodes can be detected by a single urinary test performed midafternoon or early evening of the day of the surge. This helps couples to define the interval in which conception is most likely (the 2 days prior to ovulation and the third day or day of ovulation).[24] Accuracy, reliability, and ease of use vary among the different LH detector kits. These kits are helpful for women in whom ovulation is known to occur; false positives may result in women with polycystic ovarian syndrome (PCOS), premature ovarian failure, and menopause—all conditions associated with increased LH levels.

Basal Body Temperature Charting

Basal body temperature (BBT) charting has long been used because of its simplicity. The patient is asked to record her body temperature first thing in the morning from the same site each day throughout her menstrual cycle and chart it on a BBT chart (Fig. 11.1).

The increases in progesterone associated with ovulation will lead to an increase in BBT in the days following ovulation. Biphasic patterns are characteristic in ovulatory cycles; monophasic recordings or a grossly short interval of luteal phase temperature elevation (less than 11 days) may identify patients with absent or poor quality ovulatory function. Challenges to the use of this technique are its need for a special basal body thermometer where differences of one-tenth of a degree may be easily discerned, its inconvenience (the woman must take her temperature first thing upon awakening and doing *anything* such as urinating, eating or drinking, and variability—some ovulatory women may exhibit monophasic BBT patterns), and the test cannot reliably define the time of ovulation.[25] The temperature rise seen with ovulation starts 1 to 2 days after the LH surge and lasts for 10 or more days, but because ovulation has already occurred once the increase is seen, it is too late to use the BBT chart for timing sexual intercourse for conception.

Endometrial Biopsy

Histologic evidence of secretory endometrium detected by endometrial biopsy is indicative of ovulation and corpus luteum formation. The endometrial biopsy is performed in the midluteal phase, around 7 days prior

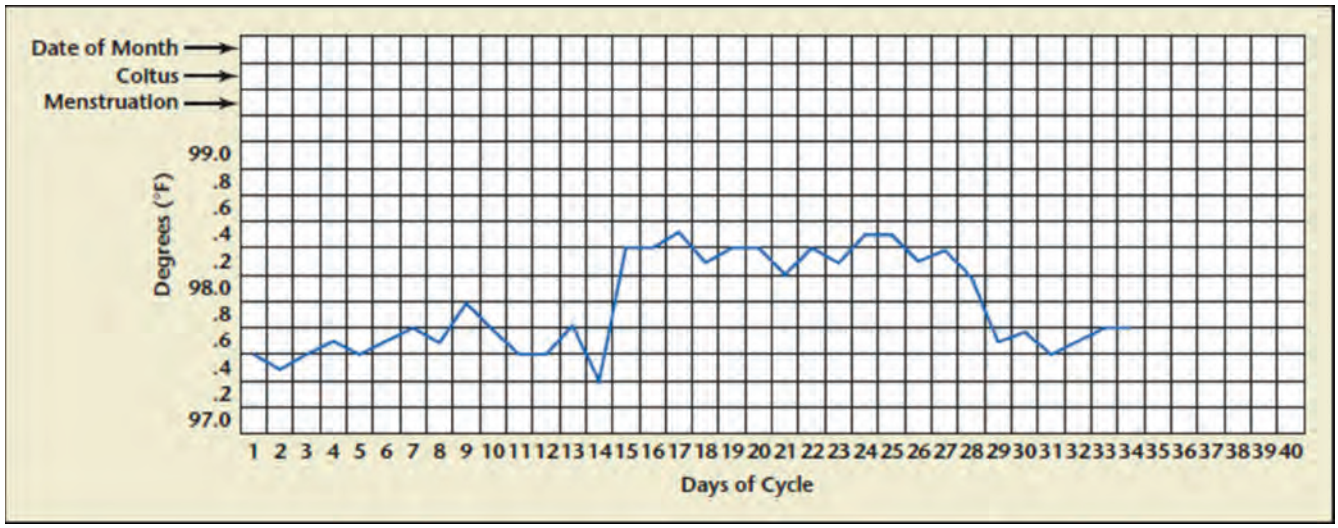

FIGURE 11.1 Example of a basal body temperature (BBT) recording chart. (From Hyde J, DeLamater J. *Understanding Human Sexuality*. 6th ed. New York: McGraw-Hill; 1997.)

to the expected period. Although the test has been used to diagnose "luteal phase deficiency" in the past, experts have moved away from this concept because of a lack of intra- and interobserver consistency; and the test is unable to provide further useful information other than the presence of ovulation.[26] Further disadvantages of endometrial sampling include expense, patient discomfort, and the known risks of the procedure.

Transvaginal Ultrasound Monitoring

The use of serial transvaginal sonography is a reliable technique to monitor follicular development. Ovulation is deemed to have occurred if the follicle reaches a mean diameter of 18 to 25 mm and subsequently changes in sonographic density or demonstrates sonographic evidence of follicular collapse. However, its use as an initial diagnostic test for all infertile women is not cost-effective.

Other Evaluation: Special Tests to Determine the Underlying Etiology

Once oligo- or anovulation has been diagnosed, additional tests aim to identify the etiology and help choose the optimal treatment. The most common causes of ovulatory dysfunction are PCOS, thyroid dysfunction, hyperprolactinemia, and late-onset congenital adrenal hyperplasia. Therefore, evaluation for PCOS should be undertaken as well as determinations of serum TSH, prolactin, and 17-hydroxyprogesterone.

Prior to instituting treatment for oligo- or anovulation, the patient undergoes ovarian reserve testing, which includes the measurement of an early follicular phase serum FSH and estradiol level. As women age, changes in the patterns and levels of gonadotropin release occur. The follicular phase shortens, and this is associated with an increase in early follicular phase serum FSH prior to any noticeable changes in peak estradiol or progesterone levels or changes in the luteal phase. A high level of FSH on day 3 (e.g., greater than 10 mIU/mL) of the cycle is associated with a poor response to in vitro fertilization (IVF), although a single measurement may not be sufficient—usually two or more high levels in different cycles is required to truly be reliable as a prognostic indicator for IVF response. It is important to note that different FSH assays may yield large variations in measurements even in the same blood sample, so it is important that providers be aware of which assay is being used if specimens go to different labs or try to send all specimens to the same lab for analysis with the same assay.

A high serum estradiol (e.g., greater than 80 pg/mL) is also associated with a poor prognosis for pregnancy after IVF and is usually associated with accelerated, premature follicle recruitment and a reduction in available oocytes. Like FSH measurements, estradiol levels vary widely with different assays.

Other tests for ovarian reserve include anti-Müllerian hormone (AMH) levels, inhibin B levels, clomiphene citrate challenge test (CCCT), exogenous FSH ovarian reserve test, and the use of ultrasound to determine antral follicle count or ovarian volume.

Treatment of Anovulatory Infertility

WHO has classified anovulation into three main groups (Fig. 11.2; Table 11.2). Women in WHO Group I have hypogonadotropic hypogonadism or hypothalamic amenorrhea. Common causes of this include central nervous system disorders such as hypothalamic or pituitary diseases, stress, eating disorders, and exercise-induced ovulatory dysfunction. Eighty percent of patients with ovulatory dysfunction will have estradiol and gonadotropin levels in the normal range and fall into the category of WHO II, eugonadotropic ovulatory dysfunction.[27]

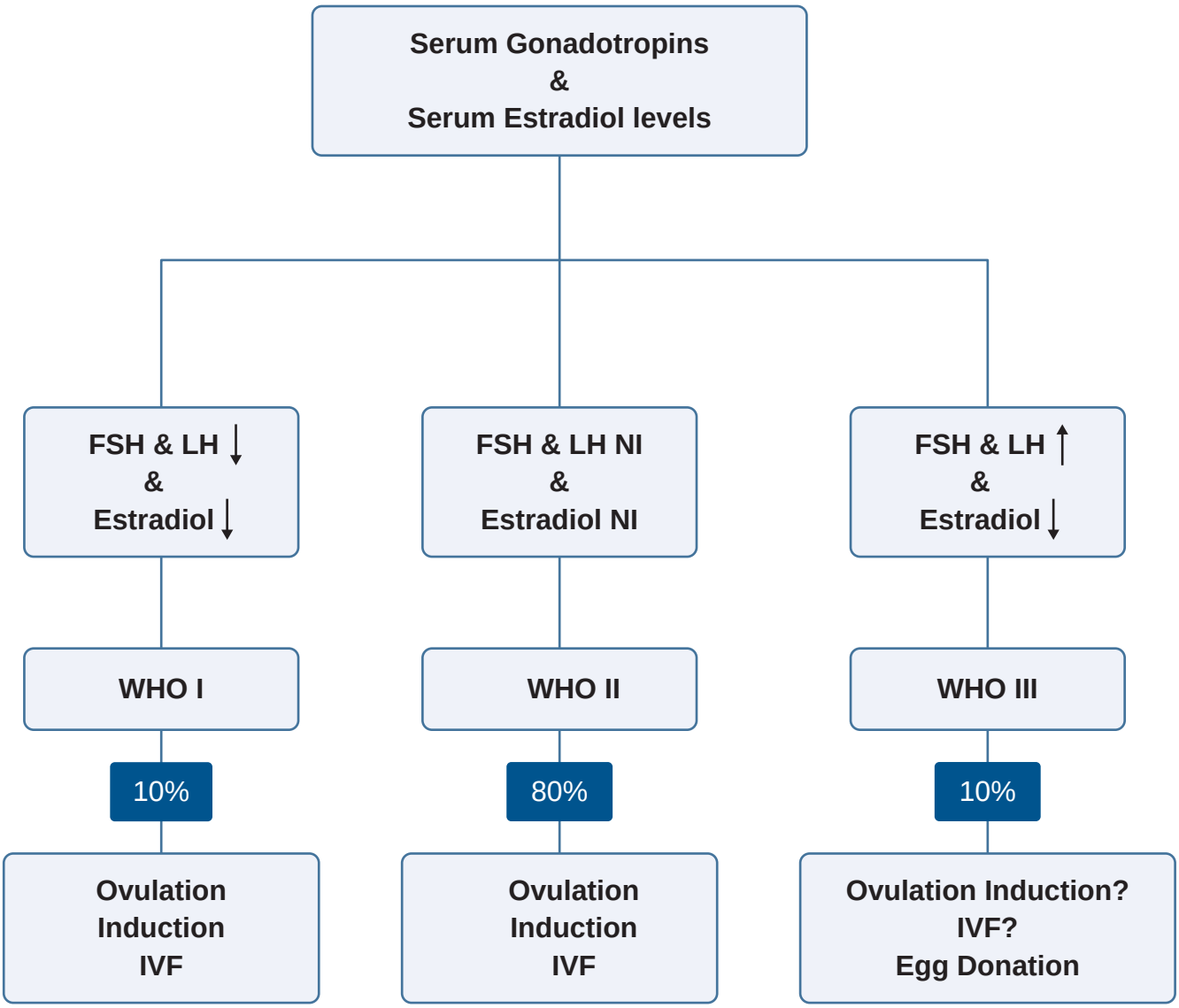

FIGURE 11.2 WHO classification of anovulation. (From Laven JS, Joop SE, Fauser BC. What role of estrogens in ovarian stimulation. *Maturitas*. 2006;54: 356–362.)

TABLE 11.2 World Health Organization Classification of Anovulation

WHO Class 1: Hypogonadotropic Hypogonadal Anovulation (Hypothalamic Amenorrhea)

These women have low or low-normal serum follicle-stimulating hormone (FSH) concentrations and low serum estradiol concentrations due to decreased hypothalamic secretion of gonadotropin-releasing hormone (GnRH) or pituitary unresponsiveness to GnRH. Other causes may include stress, eating disorders, or exercise-induced amenorrhea. Workup may include MRI of hypothalamus and pituitary region of brain.

WHO Class 2: Normogonadotropic Normoestrogenic Anovulation

These women may secrete normal amounts of gonadotropins and estrogens. However, FSH secretion during the follicular phase of the cycle is subnormal. This group includes women with polycystic ovarian syndrome (PCOS). These patients should also be screened for other causes of increased male hormones and also for metabolic disorders associated with the condition such as lipid profile abnormalities and diabetes. Some ovulate occasionally, especially those with oligomenorrhea.

WHO Class 3: Hypergonadotropic Hypoestrogenic Anovulation

The primary causes are premature ovarian failure (absence of ovarian follicles due to early menopause) and ovarian resistance (follicular form). This group may also include hyperprolactinemic anovulation.

Adapted from Agents stimulating gonadal function in the human: report of a WHO Scientific Group. *World Health Organ Tech Rep Ser*. 1973;514:1–30. http://whqlibdoc.who.int/trs/WHO_TRS_514.pdf. Accessed December 2, 2013.

(Group II is discussed in more detail later.) Group III includes hypergonadotropic hypogonadism which may be due to primary ovarian insufficiency, commonly referred to as premature ovarian failure, or to gonadal dysgenesis. The WHO also recognizes that hyperprolactinemia anovulation is a separate category, and usually the gonadotropins are normal or decreased in these cases.

Group I patients often have low body mass index (BMI) (less than 17 kg/m^2) resulting from eating disorders or excessive exercise. Mental and emotional stress may disrupt the pulsatile release of GnRH, which leads to a reduction in pituitary secretion of gonadotropin(s) and impairs ovarian function. Treatment usually involves a modification of diet, weight gain, and/or a reduction in exercise, although these approaches are not always well accepted or adhered to by patients. In patients who fail to respond to lifestyle changes, pulsatile GnRH therapy may be an option, and although it is approved for use in the United States, it is not currently available.

The majority of patients in the WHO II category have PCOS.[14] PCOS is characterized by chronic anovulation, hyperandrogenism, and insulin resistance. Diagnostic guidelines vary according to the Rotterdam criteria, the National Institutes of Health, and the Androgen Excess Society, but all include evidence of oligo- or amenorrhea and clinical or biochemical evidence of hyperandrogenism.[28]

The first line of intervention should be lifestyle change when appropriate because interventions that reduce circulating insulin levels in women with PCOS may restore normal reproductive endocrine function. In patients with BMI greater than 30 kg/m^2, weight loss and exercise is the initial recommended treatment for this etiology of anovulation.

If lifestyle intervention alone is ineffective, the first-line agent for ovulation induction in PCOS is clomiphene citrate (CC), an estrogen antagonist that increases gonadotropin release. Clomiphene is usually well tolerated; side effects include hot flushes, mood swings and (rarely) visual changes, and ovarian hyperstimulation syndrome.[29] Available evidence suggests that approximately half of the patients will ovulate on an initial CC regimen of 50 mg for 5 days starting on cycle day 3, 4, or 5 (cycle day 1 is the first day of menstruation). If the patient does not respond, the dose may be increased to 100 mg or even 150 mg.[14] In patients with very irregular menses, micronized progesterone (200 mg daily for 10 days) or medroxyprogesterone acetate (10 mg daily for 10 days) can be given and clomiphene started on cycle day 3 after initiation of the withdrawal bleed. Documentation of ovulation is made with urinary LH monitoring and/or a luteal progesterone level. If clomiphene is taken on cycle days 3 through 7, ovulation usually occurs between days 12 and 15. Typically, each dosage is tried during one menstrual cycle, with an increase in the dose for the next cycle, but recent evidence suggests that patients may be treated with a "stair-step protocol," during which the dose is increased during the same ovulation induction cycle, if no follicular activity is noted on ultrasound.[30]

If CC is not successful, the treatment choices include adjunctive use of insulin-sensitizing agents, aromatase inhibitors, gonadotropin therapy, and laparoscopic ovarian diathermy.

Insulin-sensitizing agents such as metformin (Glucophage) have been shown to increase the frequency of spontaneous ovulation, menstrual cyclicity, and the ovulatory response to clomiphene.[31,32] Many women with PCOS who are resistant to CC have demonstrable insulin resistance and hyperinsulinemia. Insulin-sensitizing agents taken alone or in combination with CC can restore ovulation. A recent multicenter trial was designed to study the question whether clomiphene, metformin, or both together should be the first-line therapy in patients with PCOS and infertility.[33] Live-birth rates were 22.5% (47 of 209 subjects) in the clomiphene group, 7.2% (15 of 208) in the metformin group, and 26.8% (56 of 209) in the combination-therapy group (p <0.001 for metformin versus both clomiphene and combination therapy; p = 0.31 for clomiphene versus combination therapy). Most experts therefore recommend that clomiphene alone should be the first-line therapy for anovulation in PCOS, with metformin added if there is evidence of hyperinsulinemia or for clomiphene-resistant patients.

Aromatase inhibitors such as letrozole block the conversion of androgens to estrogens and therefore increase gonadotropin concentrations by reducing the negative feedback on the pituitary gland. Letrozole has similar efficacy in ovulation induction as clomiphene, as demonstrated in multiple trials and meta-analyses.[34] However, a study from Canada presented as an abstract in 2005 raised concerns over its safety with respect to cardiac malformations, which led to a warning from the manufacturer of the medication. Despite the fact that subsequent studies demonstrated a comparable safety profile of the medication compared to clomiphene,[35] practitioners tend to still be cautious about the use of letrozole for ovulation induction.

Treatment with injectable gonadotropins with or without intrauterine insemination (IUI) requires close hormonal and sonographic monitoring, is costly, and has significant potential to result in multiple gestation. Laparoscopic destruction of ovarian follicles by laser or cautery has similar success rates as gonadotropin treatment but with lower multiple pregnancy rates.[36] However, risks of the procedure include the formation of adnexal adhesions and a decrease in ovarian reserve. Therefore, this procedure is usually limited to patients for whom other alternatives have been exhausted and patients who do not have access to the most costly but also most effective treatment for clomiphene-resistant PCOS patients, namely IVF.

Premature ovarian failure is defined as the development of primary hypogonadism in a woman prior to the age of 40 years. Some of these women may experience

intermittent ovulation, and 5 to 10% may conceive and deliver.[37] Premature ovarian insufficiency may be due to a variety of causes, including chromosomal defects such as Turner syndrome, fragile X permutation carriers, galactosemia, radiation exposure, certain drug exposures, and autoimmune disease. Despite a growing list of mutation associated with premature ovarian insufficiency, the etiology is still unknown in 75 to 90% of cases.[38]

In about 3% of women, the primary ovarian failure may precede the development of an autoimmune adrenal insufficiency, a potentially fatal disorder, by several years. Proper screening with serum anti-adrenal and anti-21 hydroxylase antibodies is recommended for these patients.[39] These patients are also at increased risk for developing autoimmune hypothyroidism and should be screened for this as well. Although ultrasound studies indicate that follicular development occurs frequently in these women, ovulation is infrequent.[40] Because spontaneous pregnancy rates are low in this population, treatment options include IVF with oocyte donation and adoption. The evidence to support the use of exogenous estrogen, gonadotropin therapy (with estrogen or with GnRH agonist) are fairly limited and not overly encouraging.[41–44] Success rates for the use of IVF with oocyte donation depend primarily on the age of the oocyte donor.

In patients with elevated prolactin levels, anovulation is secondary to decreased estradiol concentrations. One isolated increased prolactin level should be confirmed by repeat measurement in the early morning, avoiding recent stress or recent breast or pelvic exams, which can cause mild elevations. If the value is confirmed, hypothyroidism should be ruled out, and magnetic resonance imaging is indicated to rule out a pituitary adenoma. Treatment of hyperprolactinemic anovulation, even in the presence of a pituitary adenoma, is usually by means of dopaminergic drugs, such as bromocriptine (Parlodel). Bromocriptine is an ergot alkaloid derivative with dopamine receptor agonist activity that directly inhibits prolactin secretion.

For ovulation induction, bromocriptine is usually started at 1.25 mg orally at bedtime for 1 week and then increased to 2.5 mg twice daily. After 1 week on this dose (2.5 mg), ovulatory status should be evaluated. In the absence of ovulation, the dose can be increased in 1.25-mg increments (the maximum dosage should not exceed 100 mg/day).[45] After ovulation is established, the medication is maintained until the patient becomes pregnant. Bromocriptine is usually discontinued after a positive pregnancy test but can be used safely during pregnancy. Most patients who conceive do so within six ovulatory cycles with the average being two cycles.[46] Side effects of bromocriptine include nausea, headache, and faintness due to orthostatic hypotension. These effects are minimized by gradually increasing the dose. Taking it with food is recommended to avoid gastrointestinal side effects. Vaginal administration of bromocriptine has been associated with fewer side effects but with similar effectiveness.[47]

Another dopamine agonist, cabergoline (Dostinex), given once a week, is more effective in normalizing prolactin and restoring menses than bromocriptine and significantly better tolerated. However, given the fact that less data exist on safety in pregnancy, it has not been widely accepted as first-line therapy for ovulation induction in hyperprolactinemic patients seeking fertility.[48]

DECREASED OVARIAN RESERVE

Female fertility begins to decline many years prior to the onset of menopause despite continued regular ovulatory cycles. This occurs because of diminished oocyte quality, decreased oocyte numbers, and reproductive potential and is referred to as decreased ovarian reserve. In addition to declining fecundity, the risk of spontaneous abortion increases with a woman's age. Although age-related changes in fecundity have been documented in several populations, there is significant variability in the timing of onset of diminished reproductive potential for individual women. Although IVF was initially discovered as a treatment for tubal factor infertility, a steep rise in the number of cases performed for women older than age 40 years since 1990 made decreased ovarian reserve the most common indication for the use of assisted reproductive technology (ART) in most centers. In order to assess ovarian reserve, multiple factors must be taken into account. The most important factor in this assessment is female age, which has been shown to be inversely associated with fertility in multiple populations[49] (Fig. 11.3).

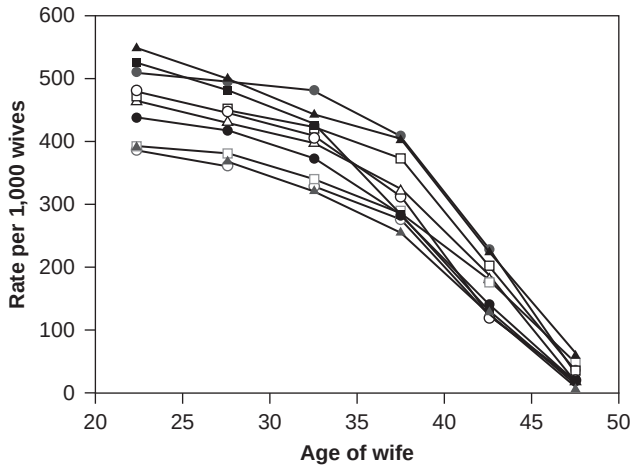

FIGURE 11.3 Marital fertility rates by age group in different populations. (From Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists; Practice Committee of the American Society for Reproductive Medicine. Age-related fertility decline: a committee opinion. *Fertil Steril*. 2008;90:S154–S155.)

The laboratory tests that have been used the longest to assess ovarian reserve are day 3 (basal) FSH and estradiol concentrations. Women with normal ovarian reserve are able to produce enough ovarian hormones from the small follicles in the early follicular phase to keep the FSH low. If there are a reduced number of follicles or oocytes, ovarian hormonal production will be low, and this will incur a rise in FSH early in the cycle. Although differences exist between laboratories, follicular phase FSH values greater than 10 mIU/mL or day 3 serum estradiol values greater than 80 pg/mL indicate poor prognosis for conception.[50] Because of the variation in FSH values between laboratories depending on the assay and methodology used, cutoff values may range from 10 to 25 mIU/mL. For this reason, clinicians should know the critical values for their respective labs. A single elevated day 3 FSH value implies poor prognosis for pregnancy, even when values in subsequent cycles are normal.[51,52]

Women with diminished ovarian reserve demonstrate premature recruitment of follicle in the menstrual cycle follicular phase. These elevated estradiol levels may inhibit pituitary FSH production yielding lower FSH levels. Measuring both the FSH and estradiol helps to avoid interpretation of a false-negative FSH test as indicative of adequate ovarian reserve.

The CCCT, another test of ovarian reserve, involves measuring day 3 FSH, administration of clomiphene 100 mg daily from days 5 to 9, and repeat FSH measurement on day 10.[53] If either the day 3 or the day 10 level is elevated (greater than 12 IU/L), decreased ovarian reserve can be diagnosed. The rationale behind this test was that women with adequate ovarian reserve should develop a cohort of follicles producing adequate estradiol and inhibin to suppress the FSH. However, given that the test is relatively involved, and with the advent of newer and more sensitive tests of ovarian reserve, the CCCT is rarely used in clinical practice nowadays. If abnormal, the day 3 FSH and CCCT tests are fairly similar in their ability to predict that pregnancy will not occur if the woman's oocytes are used. If they are normal, they are not particularly useful in predicting fertility, but they do indicate that there is an adequate ovarian reserve.

More and more commonly, ovarian reserve is assessed by measuring serum AMH concentrations.[54,55] AMH is a homodimeric disulfide-linked glycoprotein of the transforming growth factor (TGF)-β super-family produced by the granulosa cells of the preantral and small antral follicles.[56] Serum AMH concentrations have been found to be a reflection of the size of the primordial follicle pool and are highly correlated with the response to ovarian stimulation as part of ART indicative of ovarian reserve.[54,55,57] Serum AMH may be predictive of the age of onset of menopause, and concentrations are thought to be stable throughout the menstrual cycle, although this is under investigation.[58,59] It is not detectable at menopause.[60] There is no uniform agreement on the appropriate threshold value of AMH diagnostic of diminished ovarian reserve. Levels above 0.5 ng/mL are thought to represent a good reserve, whereas those less than 0.15 ng/mL are indicative of a poor response to IVF if the woman's oocytes are used.[61,62]

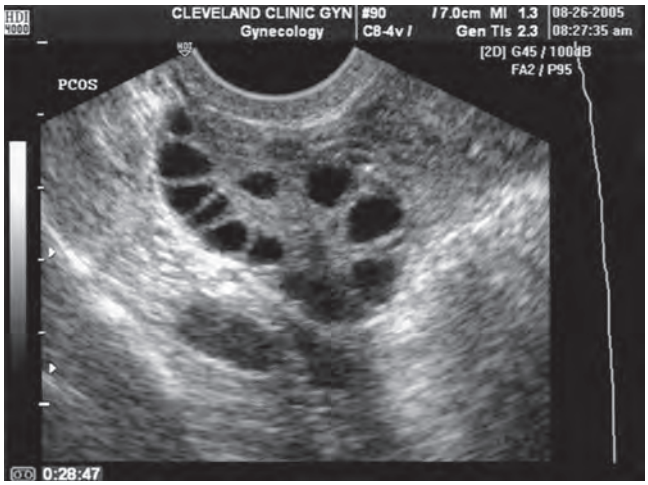

FIGURE 11.4 Transvaginal ultrasound image demonstrating antral follicles. (Reproduced with permission from Falcone T. Infertility. Disease management project. The Cleveland Clinic Center for Continuing Education. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/womens-health/infertility/. Accessed December 2, 2013. Copyright © 2000–2011 The Cleveland Clinic Foundation. All rights reserved.)

Another less commonly used serum test is the assessment of inhibin B produced by the granulosa cells of ovarian follicles. As the number of developing follicles decreases, there is a parallel decline in the serum level of inhibin B. In early menopause, the early rise in FSH is closely related to the fall in inhibin B and suggests that inhibin B may play a large role in the normal control of FSH release.[63]

Ultrasound assessment of the antral follicles in both ovaries, known as the antral follicle count (AFC), is another valuable tool when assessing ovarian reserve. Antral follicles have been defined as measuring 2 to 10 mm in the greatest two-dimensional plane[64] (Fig. 11.4).

A low AFC (suggested by some to be 4 to 10 antral follicles between days 2 and 4) has been associated with poor response to ovarian stimulation and with the failure to achieve pregnancy.[65] Age-related nomograms with normal ranges by age are being developed. Ovarian volume on ultrasound is another finding that has been correlated with ovarian reserve but is less predictive and less commonly used than the AFC.

In clinical practice, there is no one single factor to assess ovarian reserve. An integrated assessment of age as well as laboratory and ultrasound testing will be most useful to guide patient counseling and treatment.

STRUCTURAL AND ANATOMIC CAUSES OF INFERTILITY

Approximately 40% of all infertile women will demonstrate an abnormality of the uterus, cervix, and/or

fallopian tubes. To date, the best assessment of pelvic anatomic causes of infertility is with a thorough history and physical exam as well as a hysterosalpingogram.[64] Other investigations are necessary depending on patient characteristics as outlined in the following section.

Cervical Factor Infertility

The long-held belief that abnormalities of cervical mucus production or of sperm–mucus interaction are the sole cause of infertility has recently been questioned.[64] If chronic cervicitis is diagnosed on exam and upon examination of the cervical mucus, it should be treated.

Some practitioners still perform postcoital testing (PCT) by assessing the presence of motile sperm in the cervical mucus microscopically shortly after intercourse around the time of ovulation. However, the test has been found to be cumbersome for patients, poorly predictive of outcomes, subjective, and of little impact on clinical decision making. Therefore, it has largely been abandoned in clinical practice.[66,67]

Uterine Factors

Uterine factors are rarely the sole cause of infertility but may contribute to infertility in many patients. Multiple methods exist to assess the uterine cavity, looking for intracavitary lesions.

The most commonly used method in this context is the use of hysterosalpingogram (HSG). The procedure involves the insertion of 10 to 20 mL of contrast material into the uterus via a balloon catheter. Women who are allergic to shellfish or iodinated contrast agents cannot undergo HSG testing. Serial plain pelvic x-ray examination provides immediate information about the appearance of the endocervical canal, the uterine cavity, and the fallopian tube lumina[7] (Fig. 11.5).

Prophylactic antibiotics (doxycycline 100 mg twice a day for 3 days prior to the hysterosalpingogram) are warranted in women with a prior history of pelvic infection, specifically *Chlamydia*.[68] The HSG can reveal Müllerian anomalies such as unicornuate or septate uteri and intracavitary lesions such as endometrial polyps or submucosal fibroids. It can also detect the presence of intrauterine adhesions/synechiae (Asherman syndrome) and was the first imaging modality to diagnose adenomyosis noninvasively.[69] However, the sensitivity and the positive predictive value of the HSG to detect the most common lesions, polyps, and fibroids is low.[70]

Saline hysterography involves the insertion of an HSG catheter into the uterine cavity to introduce sterile saline while visualizing with the transvaginal ultrasound[71] (Fig. 11.6). This technique is thought to be more sensitive than HSG in the detection of intrauterine pathology, with higher negative and positive predictive values.[70]

The gold standard for diagnosis and treatment of intracavitary uterine lesions is hysteroscopy, which can be done in the office or in the operating room. Because this technique is more involved and costly, many authors recommend evaluation of the uterine cavity with HSG

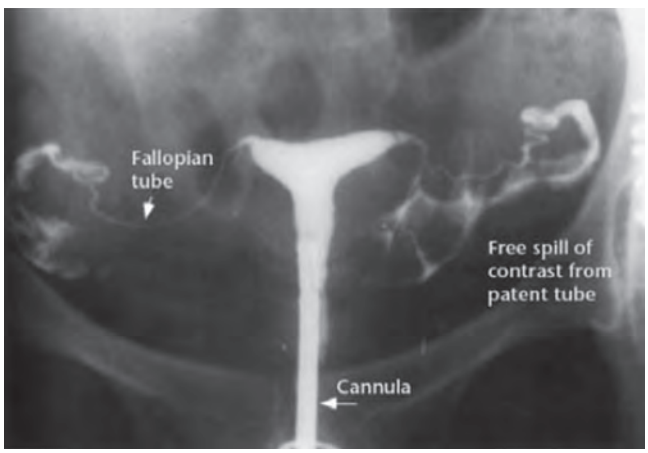

FIGURE 11.5 Example of a normal hysterosalpingogram (HSG). (From Baramki TA, Hysterosalpingography. *Fertil Steril*. 2005;83(6):1595–1606, with permission from Elsevier.)

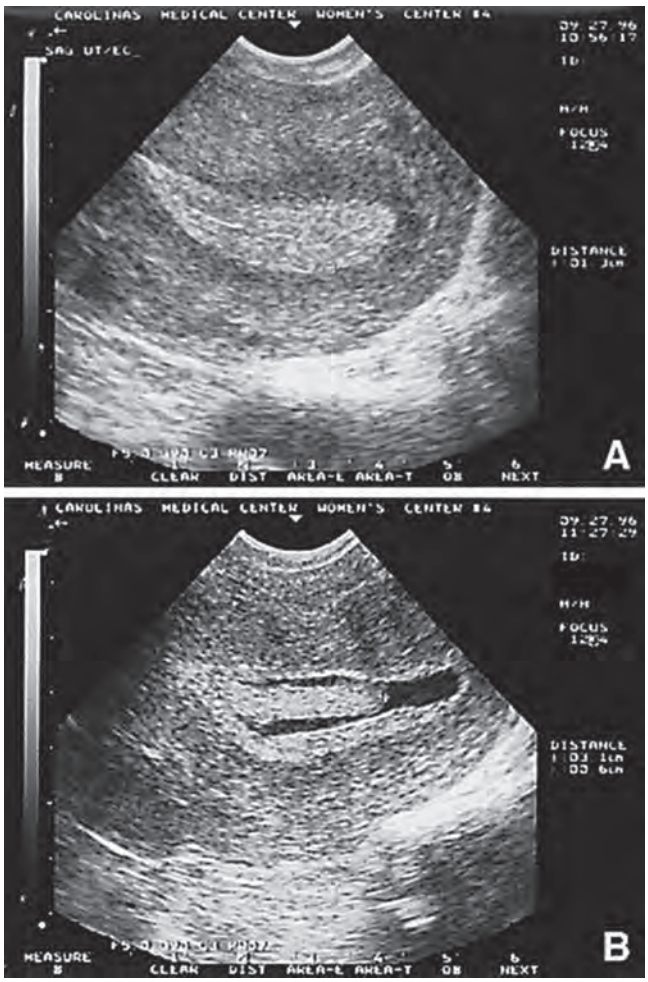

FIGURE 11.6 Example of a hydrosonogram used to detect and delineate an intracavitary lesion. (From Williams CD, Marshburn PB. A prospective study of transvaginal hydrosonography in the evaluation of abnormal uterine bleeding. *Am J Obstet Gynecol*. 1998;179:292–298.)

and saline hysterography as first-line evaluation of the infertile patient, followed by hysteroscopic evaluation if abnormalities are detected.[64,72]

Regarding therapy of intrauterine lesions, most practitioners aim to restore normal anatomy and a pristine uterine cavity prior to pursuing conception spontaneously or using ART. This concept has been well documented and studied for some conditions, whereas the evidence is weaker for other lesions such as uterine polyps. Currently, there is good evidence that intrauterine adhesions should be resected[73] and that submucosal myomas should be removed.[74] Intramural fibroids that are not impinging on the cavity but are large (greater than 5 cm in diameter) should also be removed prior to IVF.[75] According to the theory that endometrial polyps may act as intrauterine devices and impede implantation, most specialists remove any polyps found on evaluation prior to ART, even though evidence for this concept from large well-designed studies is lacking.

Tuboperitoneal Factors

The most common etiology for tubal disease causing infertility is pelvic inflammatory disease (PID), most often secondary to genital infection with *Chlamydia trachomatis*. The bacteria cause damage to the ciliated epithelium, resulting in impaired tubal transport. Many cases go undetected and untreated because 50 to 80% of women with these infections are asymptomatic.

Pelvic adhesions secondary to endometriosis or previous abdominal surgery are other etiologies of tubal distortion and dysfunction.

Therefore, historically, attempts were made to select which patients should be referred for a hysterosalpingogram (HSG) based on history, such as history of PID, pelvic surgery, or ruptured appendix, duration of infertility and infertility treatment, as well as patient age. Testing for antichlamydial antibodies was introduced to screen for and detect tubal pathology. It was shown that positive serology was moderately effective at predicting the risk of finding tubal pathology on HSG and laparoscopy, with a high negative predictive value.[76–78] However, in the evolution of the basic infertility evaluation over the years, the *Chlamydia* antibody test was found to have less and less clinical use because of its modest sensitivity for tubal disease and because of the increasing recommendation that every patient presenting for infertility evaluation should undergo HSG testing.[64] Additionally, PID can result from other pathogens, and tuboperitoneal pathology can result from other causes.

Therefore, HSG testing is the mainstay of evaluation for tubal pathology. Spill of contrast into the peritoneal cavity should be documented (see Fig. 11.5). Collection of dye around the distal tube that does not spill into the cavity with changing patient position may suggest paratubal adhesions. When tubal blockage is diagnosed on HSG, the location of the blockage is crucial. Unilateral proximal blockade with a normal contralateral tube is most often due to tubal spasm. Distal disease, together with the presence of unilateral or bilateral hydrosalpinges, as well as radiologic evidence of salpingitis isthmica nodosa, suggests PID. On delayed HSG images, the presence of a hydrosalpinx can be readily diagnosed (Fig. 11.7).

When tubal disease is suspected, diagnostic laparoscopy and chromotubation with a dilute solution of indigo carmine may be performed to gain further information about tubal status. Laparoscopy may also elucidate the etiology of tubal disease through detection of pelvic adhesions, endometriosis, and the presence of perihepatic adhesions from PID in Fitz-Hugh-Curtis syndrome.

Once tubal disease has been identified, treatment options include surgical correction of the defect(s) and, in case of bilateral complete blockage, IVF, which was originally devised for this indication.

A wide variety of tube-sparing surgical techniques have been devised. For proximal disease, excision of the uterine cornua with reimplantation of the unaffected proximal portion of the tube into the uterus[79] and hysteroscopic cannulation of the proximal tube[80] has been reported. For distal disease, laparoscopic or open techniques for distal opening of the tube ("cuff neosalpingostomy") have been described.[81] However, the risk of recurrent blockage of the hydrosalpinx is high,[82] and restoration of tubal patency does not appear to equal restoration of full tubal function, including ciliary function. Improved IVF success and suboptimal conception rates after tubal surgery have led to a drastic reduction in the number of tubal-sparing operations performed for the indication of infertility.

Clinical and basic scientific research has shown a strong negative effect of hydrosalpinges on successful conception. Inflammatory tubal hydrosalpinx fluid is thought to be embryotoxic and detrimental to

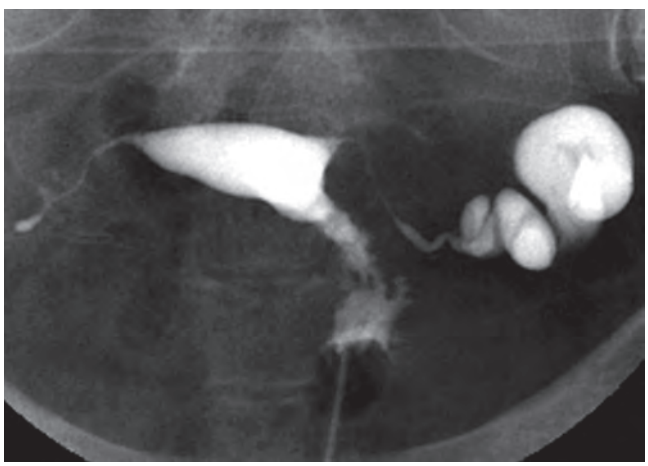

FIGURE 11.7 Hysterosalpingogram (HSG) showing the presence of a large hydrosalpinx in the left tube. (From Simpson WL Jr, Beitia LG, Mester J. Hysterosalpingography: a reemerging study. *Radiographics*. 2006;26:419–431.)

endometrial receptivity.[83] In the 1990s, it was first discovered that patients with hydrosalpinges undergoing had lower implantation and pregnancy rates[84–86] followed by the observation that salpingectomy prior to IVF improved implantation and pregnancy rates.[87,88]

Multiple well-designed randomized controlled trials (RCTs) have since confirmed that removal of hydrosalpinges prior to IVF improves implantation and pregnancy rates, and this has been validated in several meta-analyses.[89] It has also been shown that alternative surgical approaches such as proximal occlusion by proximal resection or insertion of the Essure device have the same positive effect on pregnancy rates in this setting.[90]

Therefore, the ASRM recommendation is to remove or occlude hydrosalpinges prior to IVF treatment.[91] It is unclear whether (in the case of unilateral hydrosalpinx) this concept applies to attempts at spontaneous conception as well, even though this has been advocated by some authors based on observational data.[92]

Along with the decline in rates of tubal surgery for patients with infertility over the past decade, there has been a drastic reduction in the rates of diagnostic laparoscopies for asymptomatic patients with infertility. It is well known that patients with endometriosis have higher rates of infertility and that there is a higher rate of endometriosis in the infertility population.[93] Studies have shown a modest positive effect of operative laparoscopy on pregnancy rates for asymptomatic patients with infertility.[94,95] However, it was estimated that almost 50 laparoscopies on asymptomatic patients are necessary to achieve one extra pregnancy.[93] Therefore, laparoscopy should be reserved for patients with symptoms such as pelvic pain or patients with strong historical risk factors. In asymptomatic patients with normal imaging, the yield of diagnostic and operative laparoscopy is low, and it is not considered part of the first-line infertility workup anymore.[64] In patients with indications for laparoscopy, a chromotubation and hysteroscopy may be performed at the same time, thus obviating the need for an HSG.

MALE FACTOR INFERTILITY

Male factor infertility is the only cause of infertility in approximately 30% of couples and a contributing factor in another 20 to 30%.[96] For this reason, it is important to evaluate the male partner as an integral part of the infertility workup. Evaluation of the male partner is done by history, examination, and semen analysis.

History and Physical Examination

Important elements of the history include prior paternity (although a history of fathering a prior pregnancy does not rule out semen abnormalities); a history of cryptorchidism; medical and surgical history; sexual dysfunction; and any use of medications, tobacco, alcohol, or illicit drugs.

A thorough sexual history should be taken, including timing and frequency. For an optimal chance of conception, intercourse every 48 hours during midcycle is recommended.[97]

The patient should be asked about a history of erectile dysfunction and treatment thereof. Certain lubricants can be spermatotoxic and result in impaired motility or count.[98] A history of childhood illnesses, abnormal testicular development (specifically undescended testicles), or trauma to the genitourinary organs should also be obtained. Impaired testicular function may result from any generalized insult (viremia, fever). It takes approximately 72 days for the sperm to reach the caudal epididymis after the initiation of spermatogenesis, and the effects of any adverse events may not be demonstrated in the ejaculate for 1 to 3 months. A history of a delay in pubertal development and maturation can suggest an endocrinopathy such as hypogonadotropic hypogonadism or adrenal dysfunction. Other factors contributing to impaired spermatogenesis include a history of chemotherapy or radiation, tuberculosis, exposure to environmental toxins, or drugs (specifically sulfasalazine, calcium channel blockers, cimetidine, alcohol, marijuana, and/or exogenous androgenic steroids). Elevated temperatures also impair spermatogenesis, and routine use of hot tubs or sauna should be discouraged.

On the physical examination, stigmata of systemic disease and genital abnormalities such as hypospadias, abnormally small testes, varicoceles, and absence of the vas deferens can be detected. Testicular volumes in normal men are usually in excess of 15 mL and are frequently in excess of 30 mL. Assessment for varicocele should be performed with the patient in the supine and standing positions using the Valsalva maneuver. An enlarged prostate can suggest prostatitis, which could affect semen quality. Androgen deficiency may be evidenced by decreased body hair, gynecomastia, or eunuchoid proportions. Referral to a urology or endocrine specialist may be warranted for relevant findings.

Laboratory Evaluation

Semen Analysis

The most important laboratory investigation in male infertility is the semen analysis. Although many techniques have been proposed to evaluate different etiologies of male factor infertility, only the semen analysis has proven to be a reproducible predictor of impaired fertility.

Prior to collection of the specimen, the patient is instructed to remain sexually abstinent for about 48 hours to maximize the quality of the specimen.[99] The specimen is collected by masturbation into a sterile container, collection in a spermicidal-free condom, and immediate delivery for analysis is an option offered by some

laboratories. Guidelines from WHO regarding the reference ranges for the number, morphology, and motility in a semen sample have been published and are shown in Table 11.3.[100]

A number of commercial laboratories use a variety of ranges for the different components of the semen analysis. Careful attention should be paid to these ranges, and the semen values should be interpreted in the right context.

If the semen analysis is abnormal, it should be repeated after at least 1 month by a laboratory that adheres to WHO guidelines, with a quality control program ensuring accurate testing. Although interpretation of the semen analysis results is important to the prognosis of future conception, the discriminatory ranges are not clearly defined. A study by Guzick and colleagues[101] concluded "threshold values for sperm concentration, motility, and morphology can be used to classify men as subfertile, of indeterminate fertility, or fertile. None of the measures, however, are diagnostic of infertility" (see Table 11.4).

No single category in the semen analysis can be used as a sole predictor of fertility.[102]

Some reports combine the motility and count for a total motile count (TMC):

$$\text{TMC} = (\text{sperm/mL}) \times (\%\ \text{motile}) \times (\text{volume in mL})$$

This measurement is often used to evaluate a washed specimen for IUI. Pregnancy rates are improved in specimens with a TMC exceeding 5×10^6.[103]

TABLE 11.3 Lower Reference Limits for Semen Characteristics

Lower Reference Limits (5th Centiles and Their 95% Confidence Intervals) for Semen Characteristics	
Parameter	**Lower Reference Limit**
Semen volume (ml)	1.5 (1.4–1.7)
Total sperm number (10^6 per ejaculate)	39 (33–46)
Sperm concentration (10^6 per ml)	15 (12–16)
Total motility (PR + NP, %)	40 (38–42)
Progressive motility (PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3.0–4.0)
Other Consensus Threshold Values	
pH	≥7.2
Peroxidase-positive leukocytes (10^6 per ml)	<1.0
MAR test (motile spermatozoa with bound particles, %)	<50
Immunobead test (motile spermatozoa with bound beads, %)	<50
Seminal zinc (μmol/ejaculate)	≥2.4
Seminal fructose (μmol/ejaculate)	≥13
Seminal neutral glucosidase (mU/ejaculate)	≥20

From World Health Organization. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. Geneva, Switzerland: WHO Press; 2010.

TABLE 11.4 Fertile, Indeterminate, and Subfertile Ranges for Sperm Measurements With Corresponding Odds Ratios for Infertility

	Semen Measurement		
Variable	**Concentration $\times 10^{-6}$/ml**	**Motility %**	**Morphology % normal**
Fertile range	>48.0	>63	>12
Indeterminate range	13.5–48.0	32–63	9–12
Univariate odds ratio for infertility (95% CI)	1.5 (1.2–1.8)	1.7 (1.5–2.2)	1.8 (1.4–2.4)
Subfertile range	<13.5	<32	<9
Univariate odds ratio for infertility (95% CI)	5.3 (3.3–8.3)	5.6 (3.5–8.3)	3.8 (3.0–5.0)

CI denotes confidence interval.
From Guzick DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. *N Engl J Med*. 2001;345:1388–1393.

A low semen volume in conjunction with azoospermia (no sperm) or severe oligozoospermia (severely subnormal sperm concentration) may indicate a genital tract obstruction such as a congenital bilateral absence of the vas deferens (CBAVD) and seminal vesicles or an ejaculatory duct obstruction. CBAVD is diagnosed on physical exam and is accompanied by a low semen pH, whereas ejaculatory duct obstruction is diagnosed with transrectal sonography showing dilated seminal vesicles. A low semen volume with a low sperm concentration may also be due to androgen deficiency. In some patients with a low-volume or absent ejaculate, retrograde ejaculation may be present. In order to diagnose this, a postejaculatory urinalysis should be obtained for any man whose ejaculate volume is less than 1.0 mL and who has not been diagnosed with hypogonadism or CBAVD. The analysis is performed by centrifugation and microscopic inspection of the specimen. If a diagnosis of retrograde ejaculation is made, the patient should be referred to a urology specialist.[104]

Despite its limitations, the semen analysis remains the most important tool in the investigation of male factor infertility. Endocrine abnormalities are extremely uncommon in men with normal semen parameters. If abnormalities are detected, a hormonal evaluation may be initiated, with measurements of serum FSH and serum testosterone levels as well as determination of serum LH and prolactin levels. If suggested by the physical exam, workup with transrectal or scrotal ultrasonography may reveal ejaculatory duct obstruction, varicoceles, spermatoceles, absence of the vasa, epididymal induration, and testicular masses. These should be evaluated by a urology specialist.

Specialized Tests on Semen and Sperm

No functional test has yet been validated that can unequivocally predict the fertilization capacity of spermatozoa. (In other words, nothing is more predictive

than a normal or abnormal semen analysis based on WHO criteria.) Despite this, there has been a search for other tests to improve the evaluation of the infertile male. Generally, these specialized clinical tests should be reserved only for those cases in which identification of the cause of male infertility will direct treatment.

Quantitation of leukocytes in the semen may be tested, given that an elevated number of white blood cells in the semen has been associated with deficiencies in sperm function and motility. Patients with true pyospermia (greater than 1 million leukocytes per mL) should be evaluated for a genital tract infection or inflammation.

Sperm are very immunogenic, and antisperm antibodies (ASA) may develop in the semen after specific instances, which may reduce pregnancy rates.[105] Men with a history of testicular trauma, genital infection, vasectomy reversal, or who have evidence of clumping (agglutination) on the semen analysis are candidates for ASA testing.

Sperm viability tests may identify nonmotile but viable sperm by mixing fresh semen with a supravital dye such as eosin or trypan blue or by the use of the hypoosmotic swelling test.[100] These tests may help identify viable sperm that may be used successfully for intracytoplasmic sperm injection (ICSI).

The PCT assesses the sperm–cervical mucus interaction. It involves microscopic examination of the cervical mucus shortly before expected ovulation and within hours after intercourse to identify the presence of motile sperm in the mucus. As noted previously, its use and predictive value has been seriously questioned and its use has largely been abandoned.[66,67] Other specialized tests on semen and sperm such as the zona-free hamster oocyte test and computer-aided sperm analysis (CASA) have been developed and are used by specialized laboratories. They are not part of the basic investigation of male infertility and beyond the scope of this chapter.

Genetic Screening in Male Factor Infertility

In men with azoospermia and severe oligospermia (less than 5 to 10 million sperm/mL), associated genetic abnormalities may be present, which may cause infertility by affecting sperm production or sperm transport. The three most common genetic abnormalities in this context are (a) CF gene mutations associated with CBAVD, (b) chromosomal abnormalities resulting in impaired testicular function, and (c) Y-chromosome microdeletions associated with isolated spermatogenic impairment.[104] If the evaluation reveals nonobstructive azoospermia and severe oligospermia, the patient should be informed of the potentially associated genetic abnormalities and offered genetic testing and counseling. Genetic testing for cystic fibrosis conductance regulator (*CFTR*) gene mutations in the female partner should be offered before proceeding with treatments that use the sperm of men with CBAVD, which is strongly associated with mutations of the *CFTR* gene.[106] Men with *CFTR* gene mutations may present with CBAVD, obstructive azoospermia, normal testicular volume, and normal endocrinologic values. It is estimated that 10 to 18% of men with idiopathic oligozoospermia have microdeletions of the Y chromosome. Genetic counseling should be offered to couples with microdeletions of sections of the Y chromosome in the male partner because sons of individuals with such a microdeletion would inherit it.[107]

Treatment Options for Male Factor Infertility

The treatment of severe male factor infertility including azoospermia has been revolutionized with the combination of IVF and ICSI.

Approximately 6% of infertile men have conditions for which specific therapy of confirmed benefit is available (e.g., the treatment of hypogonadotropic hypogonadism).[108,109]

Treatment of most infertile men usually involves methods to use the amount of sperm available rather than futile efforts at improving sperm concentration or motility. The treatment depends on the underlying cause and whether oligospermia or azoospermia is present. Men with obstructive azoospermia may father children either by surgical correction of the obstruction or by retrieval of sperm from the male reproductive system for IVF/ICSI.

Surgical Correction of Obstructive Azoospermia

Surgical correction may be accomplished by microsurgical reconstruction of the vas or epididymis or, in cases of ejaculatory duct obstruction, by transurethral resection of the ejaculatory ducts. Prior to proceeding with microsurgery on the male partner, the female partner should be evaluated for female infertility factors.

Reversal of a previously performed vasectomy may be performed, although the duration of obstruction and the chance for successful outcome of vasectomy reversal are inversely related.[110]

Varicocele Repair

Varicoceles are found in 15% of normal men and in approximately 40% of men presenting with infertility.[104] Although varicoceles are associated with infertility, many men with varicoceles father children. Experimental data from clinical and animal models suggest that varicoceles have a deleterious effect on spermatogenesis, possibly secondary to elevated testicular temperature and venous. Surgical varicocele repair is performed through an inguinal or subinguinal approach employing an operating microscope for optical magnification or by percutaneous embolization therapy.

The literature is replete with studies both supporting and opposing the view that varicocele repair results in increased pregnancy rates. Experts suggest that

varicocele treatment should be offered to the male partner of a couple attempting to conceive when all of the following factors are present: (a) a varicocele is palpable, (b) the couple has documented infertility, (c) the female partner has normal fertility or potentially correctable infertility, and (d) the male partner has one or more abnormal semen variables or abnormal results on sperm function tests.[104] The majority of studies indicate that semen quality improves in a majority of patients after varicocele repair.[111,112] Some studies also report a favorable effect on fertility, although this is an inconsistent finding in the literature and matter of debate.[113] An individualized approach is warranted, and guidelines for referral to a urologist are available.[114]

Assisted Reproductive Techniques for Male Infertility

Intrauterine Insemination

In patients with oligospermia of the male partner and a normal evaluation of the female partner, controlled ovarian hyperstimulation (COH) combined with IUI of prepared spermatozoa may be attempted. IUI is performed after separation of motile from nonmotile spermatozoa and other material in the seminal plasma that might have detrimental effects on fertilization. This may result in increased pregnancy rates in couples with male subfertility.[115]

In Vitro Fertilization/Intracytoplasmic Sperm Injection

The advent of IVF combined with ICSI has revolutionized the treatment for couples whose infertility is secondary to severe oligospermia or azoospermia. ICSI should be used in almost all cases in which sperm are retrieved from the testes or epididymis of a man with obstructive azoospermia because these techniques very rarely produce enough motile sperm for IUI or standard IVF.[116] ICSI results in high fertilization and clinical pregnancy rates when surgically retrieved epididymal or testicular spermatozoa are used.

Sperm retrieval in men with obstructive azoospermia may be performed through an open operation or percutaneously. The sperm may be obtained from a testicular, epididymal, vasal, or seminal vesicular location, depending on the experience and preference of the urologist performing the retrieval. Sperm retrieval may be performed before or simultaneously with egg retrieval from the female partner. There is currently no evidence for differences in ICSI outcomes between the use of cryopreserved and fresh sperm.[104] If retrieval of any viable sperm for ICSI is impossible, therapeutic donor insemination may be considered by the couple. Because of the involved emotional, ethical, and legal issues, detailed counseling should be offered prior to proceeding with this option.

UNEXPLAINED INFERTILITY

Unexplained infertility is a diagnosis of exclusion. A diagnosis of unexplained infertility is made after standard investigations (semen analysis, laboratory assessment of ovulation, uterine cavity and tubal patency assessment, and evaluation of ovarian reserve) fail to reveal any abnormality. Although estimates vary, the likelihood that an infertile couple has unexplained infertility is approximately 15 to 30%.[7,117] The likelihood of pregnancy without treatment among couples with unexplained infertility is less than that of fertile couples but greater than zero.

It is possible that unexplained infertility represents the lower extreme of the normal distribution of fertility with no defect present. The diagnosis may also be assigned to couples for which the routine infertility evaluation misses subtle defects because of imperfect or incomplete testing methods. Studies of couples with unexplained infertility who are followed without any treatment report a broad variation in cumulative pregnancy rates. It has been estimated that without treatment, up to 60% of couples with unexplained infertility will conceive within 3 years.[118]

A retrospective review of 45 studies by Guzick and colleagues[119] found an average cycle fecundity of 1.3 to 4.1% in the untreated groups, which was lower than most treatment interventions.

Treatment Options for Unexplained Infertility

In couples with unexplained infertility, no specific defect or functional impairment is evident. Therefore, by definition, the treatment for unexplained infertility is empiric. The principal treatments for unexplained infertility include expectant observation with timed intercourse and lifestyle changes, CC and IUI, COH with IUI, and IVF. The role of operative laparoscopy is controversial, as discussed in the following section. Commonly, the treatment approach is to move sequentially from therapies requiring lower resources (expectant management) to those requiring more resources.

Expectant Management

Expectant management with timed intercourse and lifestyle changes is associated not only with the lowest cost but also the lowest cycle fecundity rates.

Epidemiologic evidence suggests that cigarette smoking, abnormal BMI, and excessive caffeine and alcohol consumption reduce fertility in the female partner. Therefore, the female partner should be counseled to achieve a normal BMI, reduce caffeine intake to no more than 250 mg daily (two cups of coffee), and reduce alcohol intake to no more than four standardized drinks per week.[120] The couple is then advised to time intercourse during the window of fertility, identified by BBT recordings, urinary LH ovulation predictor kits, or midluteal

serum progesterone testing. Increasing age of the female partner negatively affects the pregnancy rate associated with expectant management.[121] For couples who are young, have no tubal or sperm problems, that is, they have a good prognosis for fertility as well as those with an intermediate prognosis for fertility, expectant management for 6 months achieved the same ongoing pregnancy rate as that achieved with IUI with gonadotropin injections.[122,123] Therefore, expectant management may provide an option for a couple with unexplained infertility in whom the female partner is young and the problem of oocyte depletion is not an immediate concern.

Operative Laparoscopy

The role of operative laparoscopy in the treatment of unexplained infertility and possible subclinical endometriosis is currently unclear. In 1997, a Canadian group reported the results of an RCT in a population of 341 infertile women 20 to 39 years of age with minimal or mild endometriosis.[95] Women were randomly assigned to undergo resection or ablation of visible endometriosis or diagnostic laparoscopy only and followed for 36 weeks after the intervention. Fifty of the 170 women became pregnant in the intervention group, compared with 29 of 169 in the diagnostic laparoscopy group corresponding to fecundity rates of 4.7 and 2.4 per 100 person-months. This led the authors to conclude that "laparoscopic resection or ablation of minimal and mild endometriosis enhances fecundity in infertile women."

However, a smaller RCT from Italy with a similar study design could not confirm these results.[124] The conclusion of a Cochrane review on the topic was that laparoscopic surgery in the treatment of minimal and mild endometriosis may improve pregnancy success rates but that the "relevant trials have some methodological problems and further research in this area is needed."[94] Therefore, if laparoscopy is performed in a patient with unexplained infertility and minimal or mild endometriosis is identified, ablation of endometriosis should be performed. However, the current literature does not support routine diagnostic laparoscopy in all patients with unexplained infertility.

Intrauterine Insemination

For IUI, washed sperm is placed into the upper uterine cavity around the time of ovulation. The washing is done to remove prostaglandins. It can be performed in conjunction with natural ovulation timed with LH kit, ovulation induction using CC, or injectable gonadotropins. IUI without COH is not routinely performed in couples with unexplained infertility because the available data suggest that it is inferior to IUI with ovulation induction with respect to the outcome of live birth rates.[125,126]

Both CC and gonadotropins have been used for COH in the treatment of unexplained infertility in combination with IUI or alone. COH in women with a normal ovulatory assessment may overcome subtle ovulatory defects missed by standard testing, and an increased number of eggs available for fertilization may increase the likelihood of pregnancy. In a similar fashion, introducing washed sperm into the uterine cavity using IUI may increase the density of motile sperm available to ovulated oocytes, which should maximize the chance of fertilization. Gonadotropin therapy is superior to CC therapy, and both are most effective when combined with IUI.[119]

Controlled Ovarian Hyperstimulation

The available evidence suggests that the use of CC alone with timed intercourse in patients with unexplained infertility results in only one additional pregnancy per 40 cycles performed, whereas CC with IUI has a pregnancy rate per cycle of 9.5%.[117,127] In contrast, the pregnancy rate per cycle is 8% with gonadotropin treatment alone and 18% with gonadotropin treatment combined with IUI.[119] The primary complication with COH is multifetal gestations; in instances where CC is used for COH, the risk of twins is approximately 7 to 8%. In COH using gonadotropin treatments, the risk of multiple gestations is increased, as is the risk of ovarian hyperstimulation. The rate of multiple gestations varies from 14 to 39%.[128] With an increasing number of COH/IUI cycles, the cumulative pregnancy rate rises. However, the evidence suggests that the number of COH/IUI cycles prior to consideration of IVF treatment should be limited to three cycles.[126] Multiple treatment cycles are not beneficial in older women.

In Vitro Fertilization/Intracytoplasmic Sperm Injection

IVF with or without ICSI is the most expensive but also most successful treatment of unexplained infertility. Therefore, it is the treatment of choice for unexplained infertility when the less costly but also less successful treatment modalities outlined earlier have failed. The ASRM Practice Committee published an analysis on the appropriate roles and the cost-effectiveness of the various procedures in the management of unexplained infertility by analysis of previously published data.[117,119]

It appears that there is a correlation between the cost of a treatment modality and its pregnancy rates. Studies on the cost-effectiveness of various treatments are underway. A commonly used approach is to attempt COH with IUI first, with transition to IVF/ICSI if pregnancy is not achieved in a timely manner.

A recently published RCT examined the role of "fast-tracking" patients with unexplained infertility to treatment with IVF without a previous trial of COH/IUI.[129] In

this Fast Track and Standard Treatment trial, Reindollar and colleagues[129] assigned 503 couples with unexplained infertility to either conventional infertility treatment or an accelerated track to IVF. Patients were randomized to receive either a conventional treatment regimen of three cycles of clomiphene/IUI, three cycles of FSH/IUI, and up to six cycles of IVF or to receive an accelerated treatment course of three cycles of CC/IUI and then up to six cycles of IVF. An increased rate of pregnancy and a lower median time to pregnancy (8 months compared to 11 months) were observed in the accelerated arm compared with the conventional arm. Average charges per delivery were $9,800 lower in the accelerated arm compared to conventional treatment, leading the authors to conclude that the FSH/IUI cycles were of no added value. These findings may affect future practice patterns in the treatment of unexplained infertility.

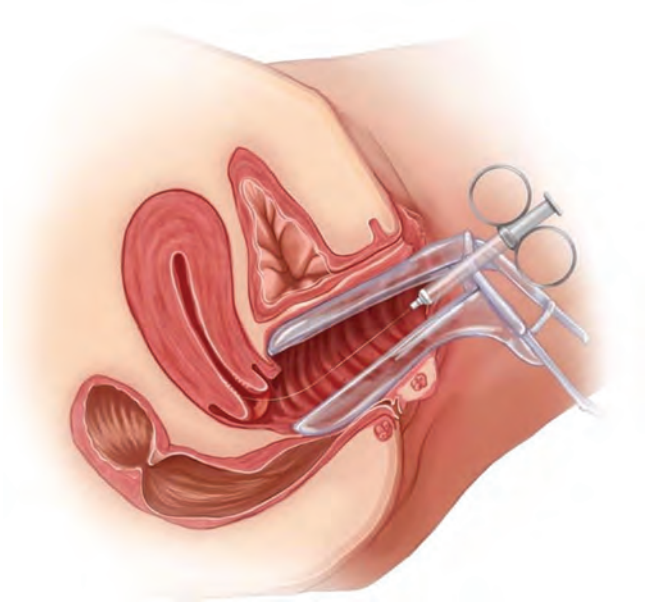

FIGURE 11.8 The principle of intrauterine insemination (IUI). Washed and prepared sperm is placed directly into the uterus around the time of ovulation, bypassing the cervix and increasing the chances of pregnancy. (From Ricci S. *Essentials of Maternity, Newborn, and Women's Health Nursing.* 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2008.)

OVERVIEW OF ASSISTED REPRODUCTIVE TECHNOLOGY (ART) AND ELECTIVE SINGLE EMBRYO TRANSFER

In this chapter, reference is made at multiple points to the most frequently used techniques in ART. This section serves as an introduction to these techniques and to a selected topic of great importance in the field of ART, elective single embryo transfer.

Intrauterine Insemination

IUI is a technique that involves the introduction of washed sperm into the uterine cavity around the time of ovulation (Fig. 11.8).

It can be done as part of a natural (unmedicated) or stimulated cycle. Medications for ovarian stimulation included CC, letrozole, and injectable gonadotropins. The timing of the procedure is determined by having the patient use LH ovulation predictor kits or by triggering ovulation with recombinant human chorionic gonadotropin (hCG). The latter approach is more costly and time consuming, and one study was not able to demonstrate a consistent benefit for the use of hCG-induced ovulation compared with spontaneous ovulation as ascertained by urinary LH testing for the timing of IUI.[130]

In Vitro Fertilization

IVF has revolutionized the field of infertility treatment. Louise Brown, born in the United Kingdom in 1979, was the first successful case of IVF described in a landmark publication from 1980.[131] This discovery eventually led to the authors being awarded the Nobel prize. Initially, oocytes from patients were retrieved laparoscopically. The technique of IVF has since evolved and been refined in many aspects. The primary determinant of the success of IVF is the age of the woman (Fig. 11.9). This is due to the decreased ovarian responsiveness to gonadotropin stimulation that accompanies aging as well as a decreased number of oocytes available for IVF and a decreased implantation rate due to poor egg quality.[132] Many programs will not perform IVF without donor eggs once a woman is around 41 to 45 years of age, although the upper age limit for IVF without donor eggs remains controversial.

The main steps of the IVF process are ovarian downregulation, ovarian stimulation, oocyte aspiration, and embryo transfer (ET). Ovarian downregulation is usually achieved with combined oral contraceptive pills and/or GnRH agonist preparations. Ovarian stimulation is primarily achieved with injectable recombinant gonadotropins; supraphysiologic doses are often used to overcome the natural suppression of follicular growth that is usually mediated by the dominant follicle. This leads to a hyperstimulated ovarian appearance on ultrasound (Fig. 11.10).

Achieving the right balance between too little and too much stimulation of the ovaries is crucial in this process termed "controlled ovarian hyperstimulation." If the ovaries are not stimulated enough, the patient may only develop a small number of follicles and end up with few or no oocytes available for fertilization and transfer. If, however, the patient gets stimulated too aggressively, she is at risk for "ovarian hyperstimulation syndrome" (OHSS), a dangerous complication of COH.[133] In OHSS, luteinization of the many follicles in the enlarged ovaries leads to an acute fluid shift out of the intravascular space. This phenomenon, now thought to be mediated primarily by vascular epithelial growth factor, leads to

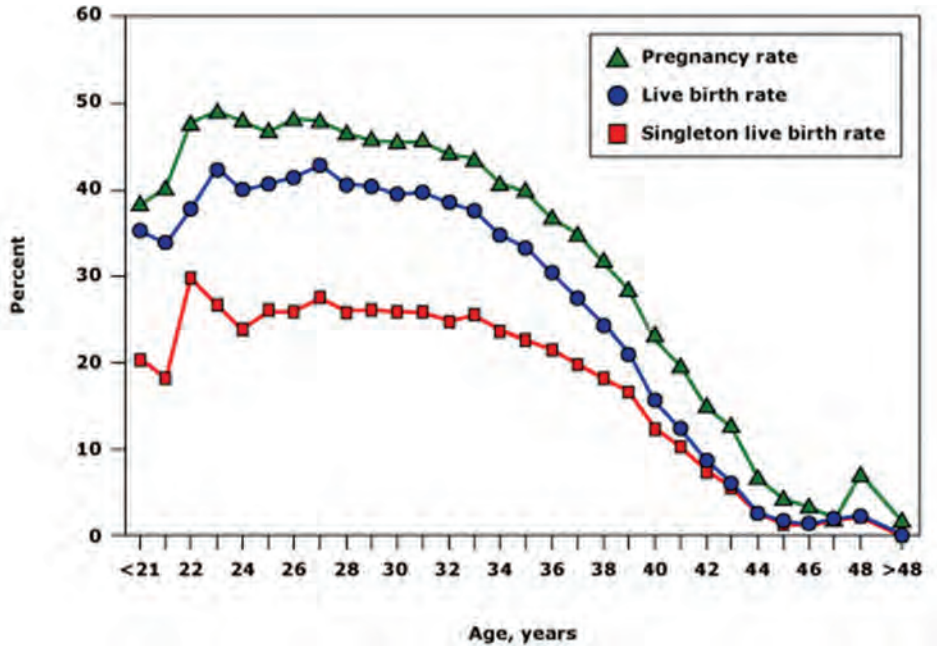

FIGURE 11.9 The above figure shows the percentages of pregnancies, live births, and singleton live births for women of different ages who had ART procedures using fresh nondonor eggs or embryos in 2006. The percentages of ART cycles resulting in live births and singleton live births are different because of the high percentage of multiple-infant deliveries counted among the total live births. The percentage of multiple-infant births is particularly high among women younger than 35 years. Among women in their 20s, the percentages of ART cycles resulting in pregnancies, live births, and singleton live births were relatively stable; however, success rates declined steadily from the mid-30s onward. *For consistency, all percentages are based on cycles started. (From Centers for Disease Control and Prevention; American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. *2006 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports.* Atlanta, GA: Centers for Disease Control and Prevention; 2008.)

hypovolemia, hemoconcentration, and third-space accumulation of fluid.[134] In its most severe form, the third spacing may lead to renal failure, hypovolemic shock, thromboembolic episodes, acute respiratory distress syndrome, and death. Therefore, reproductive endocrinologists take multiple precautions to prevent OHSS. The most important one is careful and close monitoring of the patient undergoing COH by following follicle numbers and sizes by ultrasound and close monitoring of the estradiol concentrations, a marker of follicle growth. A cycle may be cancelled if there is poor or excessive ovarian response.

Following COH, once adequate follicular growth has been achieved (demonstrated by two or more follicles with a mean diameter of 18 mm or more and a serum estradiol level of 200 pg/mL), the final maturation of the oocytes is achieved with an "hCG trigger." This is the administration of injectable hCG, either recombinant or urinary hCG. A dose of 250 mcg of recombinant hCG appears to be equivalent to the standard dose of urinary hCG of 5 to 10,000 units.[135] Because hCG has a long half-life, one of the concerns associated with its use is OHSS. Recombinant hCG has a shorter half-life than urinary hCG. Some practitioners use a dose of LH between 15,000 and 30,000 IU because there is some evidence that it is as effective as hCG but has a lower risk of OHSS.[136] GnRH agonists have been used to trigger ovulation and are associated with less OHSS; however,

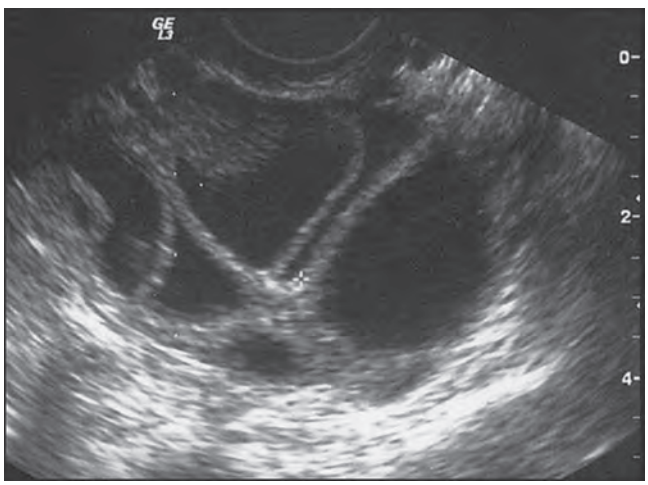

FIGURE 11.10 Appearance of hyperstimulated ovaries on transvaginal ultrasonograph. (From American Society for Reproductive Medicine. *Assisted Reproductive Technology. A Guide for Patients.* Birmingham, AL: Author; 2011. http://www.reproductivefacts.org/uploadedFiles/ASRM_Content/Resources/Patient_Resources/Fact_Sheets_and_Info_Booklets/ART.pdf. Accessed December 2, 2013.)

they are also associated with significantly lower pregnancy and live birth rates compared to hCG.[137]

Once the ovulation trigger is given 34 to 36 hours after this injection, oocytes are recovered by transvaginal ultrasound-guided follicle aspiration 34 to 36 hours later (Fig. 11.11). This may be done with intravenous propofol or some other type of analgesia/anesthesia, or conscious sedation or a regional block. The prophylactic use of antibiotics is advocated to reduce the risk of infection.

Following oocyte retrieval, insemination of the oocytes occurs either by conventional insemination or by ICSI. For ICSI, a single sperm is directly injected into each mature egg. This technique has revolutionized the treatment of male infertility but is also increasingly used routinely in nonmale factor cases for 50 to 100% of oocytes in many centers (Fig. 11.12).

Fertilization of the oocyte is confirmed by finding two pronuclei in the zygote about 17 hours after insemination or ICSI. Successfully fertilized oocytes become embryos and are grown in the embryology laboratory until the day of ET. The ET is most often done on day 3 after fertilization, although transfer at the blastocyst stage (days 5 to 6 after fertilization) may be done in selected cases, and clinical research to assess the superiority of each approach is ongoing.

In the process of pregnancy, the embryo grows to a point where it breaks through the zona pellucida, which

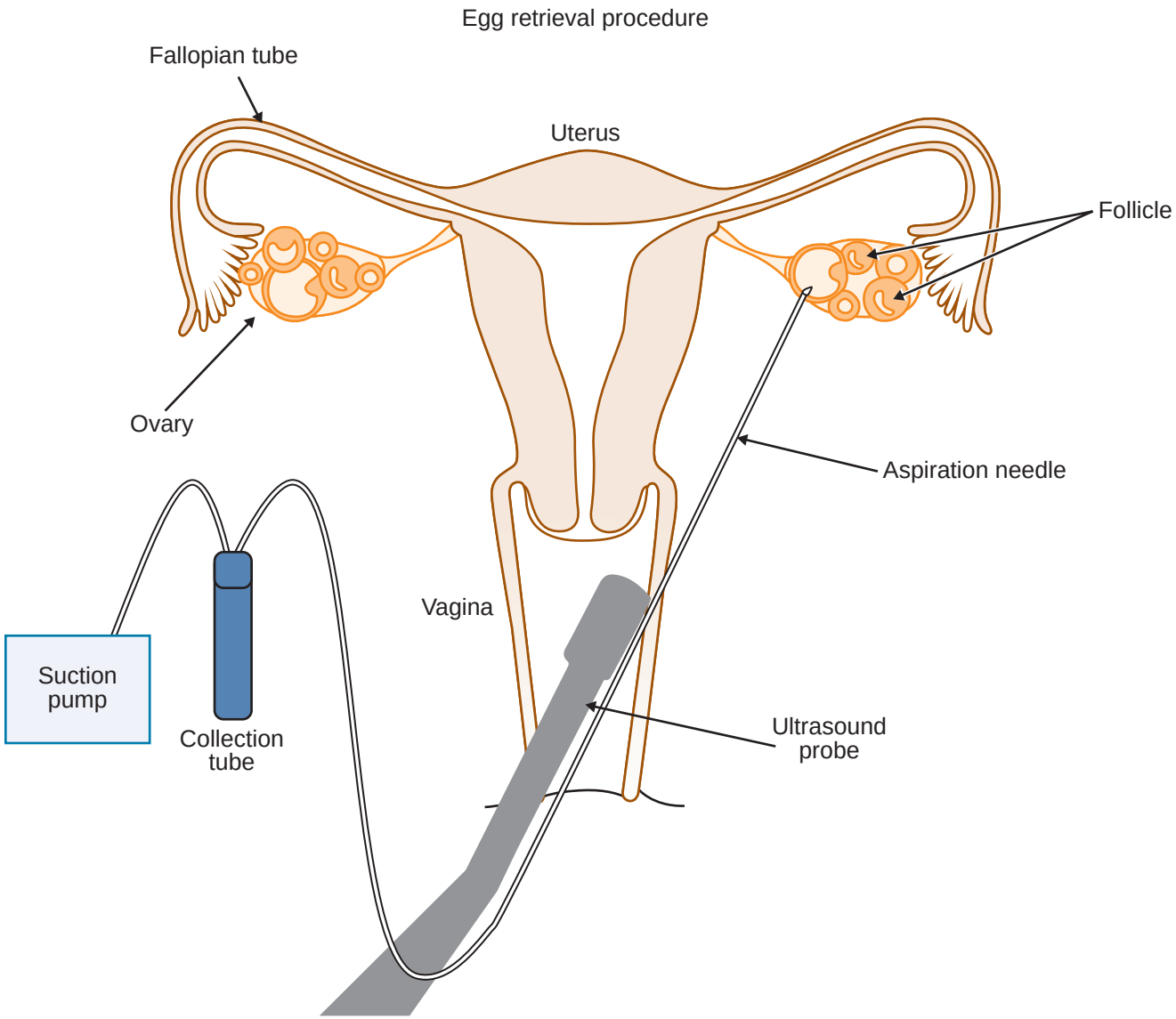

FIGURE 11.11 Transvaginal ultrasound-guided follicle aspiration. (From American Society for Reproductive Medicine. *Assisted Reproductive Technology. A Guide for Patients.* Birmingham, AL: Author; 2011. http://www.reproductivefacts.org/uploadedFiles/ASRM_Content/Resources/Patient_Resources/Fact_Sheets_and_Info_Booklets/ART.pdf. Accessed December 2, 2013.)

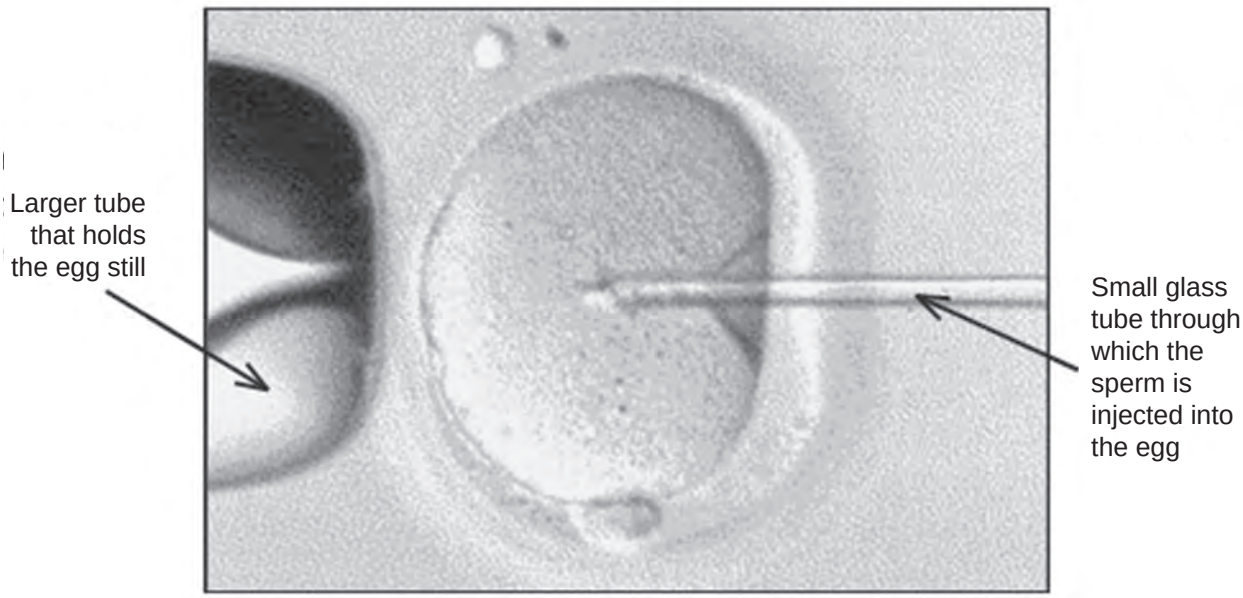

FIGURE 11.12 The technique of intracytoplasmic sperm injection (ICSI). (From American Society for Reproductive Medicine. *Assisted Reproductive Technology. A Guide for Patients*. Birmingham, AL: Author; 2011. http://www.reproductivefacts.org/uploadedFiles/ASRM_Content/Resources/Patient_Resources/Fact_Sheets_and_Info_Booklets/ART.pdf. Accessed December 2, 2013. Copyright© 2011 by the American Society for Reproductive Medicine. All rights reserved. No part of this presentation may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage and retrieval system without permission in writing from the American Society for Reproductive Medicine, 1209 Montgomery Highway, Birmingham, AL 35216.)

allows it to implant on the endometrial surface; this is a process known as "hatching." "Assisted hatching" is a laboratory procedure where the zona pellucida is chemically or mechanically opened in the 3-day embryo so that in the upcoming days, the embryo may hatch from the zona. It is thought this may improve the percentage of embryos that implant, but its use is controversial.[138] Most programs transfer embryos to the uterus about 72 hours after egg retrieval (at the four to eight cell cleavage stage) with transfer at day 5 (the blastocyst stage) being the next most common time of transfer. Delaying transfer to day 5 allows for preimplantation genetic diagnosis (PGD) to be done, but there is no strong evidence base that there is any other major advantage to waiting for the blastocyst stage to transfer.

Embryos are placed into the top of the uterus or the fallopian tubes via a small catheter. The experience of the practitioner is a major factor in the success of the procedure. Although commonly recommended, there is no evidence that bed rest posttransfer improves the implantation rate nor is there evidence that any sort of "embryo glue" improves implantation.[139,140] In the United States, the number of embryos transferred is not regulated by law, although the ASRM has published guidance on this issue.[141]

Endometrial receptivity plays a major role in the success or failure of embryo implantation after IVF. It is common practice to attempt to enhance this receptivity by administering a progesterone supplement during the luteal phase. This is generally started on the day of oocyte retrieval or ET.[142,143] There is no uniform agreement on the optimum duration of supplementation. Intramuscular progesterone or other progesterone preparations appear to have equal effectiveness although oral progesterone does appear to be less effective.[144,145]

Supernumerary embryos obtained as part of the IVF process are cryopreserved. Both slow freezing and ultrarapid freezing (vitrification) are safe and effective for embryo cryopreservation. About 10 to 20% of embryos do not survive the thawing process. Many studies have found that children born after transfer as a frozen-thawed embryo have better perinatal outcomes compared to those born after transfer as a fresh embryo. This is reflected in lower rates of preterm birth, lower birth weights, growth restriction, and perinatal mortality.[146,147] The specific reasons or mechanisms for this are not known although lower endometrial receptivity at the time of fresh transfer due to ovarian stimulation or evidence of a better embryo quality by virtue of surviving freezing and thawing have been suggested. There is no evidence of a maximum duration of storage.

The first blood test for identification of hCG is usually done no sooner than 12 days after egg retrieval. If hCG was used to trigger ovulation, it is usually cleared within 2 weeks, which is about 12 days after retrieval, so it should not interfere with pregnancy testing. Serial hCG tests are done to monitor if the pregnancy is developing intrauterine and normally. If the hCG is positive but there is no evidence of an intra- or extrauterine pregnancy and menses occurs at the expected time, it is termed a "chemical pregnancy."

Failure may occur at any step in the IVF process, and the reason for failure is usually not known. If viable embryos are produced, the failure is generally due to a

lack of implantation, and this may be related to poor egg quality, diminished endometrial receptivity, or transfer efficiency issues.

Concerns over a potential increased risk for ovarian cancer related to the use of fertility drugs have been raised. The risk of ovarian cancer is, however, elevated in women with infertility because of the lower number of pregnancies experienced by this group of women. Most reviews have not found a strong evidence base for infertility treatment as an independent factor for ovarian cancer.[148,149] More studies are needed to further elucidate the relationship, if any, between the various forms of infertility therapy and ovarian malignancy.

There is no clear evidence that IVF increases a woman's risk of developing breast cancer.[148,150,151]

Elective Single Embryo Transfer

ART has revolutionized the treatment of infertility and given millions of couples who had difficulty conceiving the chance to start a family. However, it has also introduced a significant increase in the number of "multiple pregnancies," including twins and "higher order multiple" (HOM) pregnancies consisting of three or more implanted embryos.[152] There is overwhelming evidence that multiple pregnancies represent a major threat to the health of the mother and the fetuses. Most complications of pregnancy, such as pre-eclampsia, preterm labor, and diabetes of pregnancy, are more common in multiple pregnancy compared to singletons, and the rate of babies born prematurely is much higher. Because of the increased risks to the mother and the infants, physicians try to prevent multiple pregnancy as much as possible. When HOM pregnancies occur, it is possible to reduce the risks for the mother and the fetus by performing a procedure called "multifetal pregnancy reduction," whereby the pregnancy is reduced to a singleton or twin pregnancy under ultrasound guidance. However, despite a risk reduction achieved from this procedure, the risk to the pregnancy remains higher than the risk of a pregnancy starting out as a singleton or twin pregnancy.[153] In addition, the procedure may result in inadvertent loss of the entire pregnancy, and even if this is not the case, the psychological consequences of facing this procedure are significant for any couple. For many couples, multifetal reduction is not an option because of religious, cultural, or personal reasons.

In view of this background, the ASRM and the Society for Assisted Reproductive Technology (SART) have issued guidelines for the number of embryos transferred in an IVF cycle.[154] The recommendations for the number of transferred embryos are influenced by multiple factors, including patient age and embryo quality. The guidelines are not meant as strict rules but more as a help for patients and physicians—ASRM/SART[154] state that "*Strict limitations on the number of embryos transferred, as required by law in some countries, do not allow treatment plans to be individualized after careful consideration of each patient's own unique circumstances.*" However, every IVF program is asked to submit its statistics to a central database, and programs with an especially high multiple pregnancy rate may be subject to a SART audit.

When deciding on the number of embryos to transfer, clinicians consider what their patients' prognosis for success is. The prognosis is considered "favorable" if it is the first IVF cycle, the embryos are good quality (as determined by the embryologist monitoring them), and there are surplus embryos available for freezing. The prognosis is also considered "favorable" if the couple had a previous IVF success. It is important for the couple and their physician to have a good discussion about how many embryos to transfer, so that the best outcome can be achieved after the couple makes an informed decision. Table 11.5 summarizes the ASRM/SART guidelines.[154] It can be noted that in general, the recommendation is to transfer less embryos if the transfer occurs at the blastocyst stage (days 5 to 6 after fertilization) than if the transfer occurs at the cleavage stage (days 2 to 3 after fertilization). The reason for this is that if an embryo can reach the blastocyst stage in the laboratory, it should have a higher chance of implanting.

It should also be noted that the number of transferred embryos goes up with age. Physicians can also increase the number of transferred embryos when previous IVF cycles were unsuccessful. In donor egg IVF cycles, the age of the donor is used to determine how many embryos should be transferred into the recipient. In frozen ET cycles, the "number of good quality embryos transferred should not exceed the recommended limit of fresh embryos for each age group.

ASRM and SART have also recently issued a "committee opinion" on a phenomenon that has attracted great

TABLE 11.5 American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Guidelines on the Number of Embryos to Transfer

	Age			
Prognosis	**< 35 yrs**	**35–37 yrs**	**38–40 yrs**	**41–42 yrs**
Cleavage-stage embryos[a]				
Favorable[b]	1–2	2	3	5
All others	2	3	4	5
Blastocysts[a]				
Favorable[b]	1	2	2	3
All others	2	2	3	3

[a]See text for more complete explanations. Justification for transferring one additional embryo more than the recommended limit should be clearly documented in the patient's medical record.

[b]Favorable = first cycle of IVF, good embryo quality, excess embryos available for cryopreservation, or previous successful IVF cycle.

From Practice Committee of the American Society for Assisted Reproductive Medicine. Guidelines on number of embryos transferred. *Fertil Steril.* 2009;92:1518–1519.

attention in the field of assisted reproduction—"elective single embryo transfer" (eSET).[155]

eSET is defined as the transfer of a single embryo at the cleavage (days 2 to 3) or blastocyst (days 5 to 6) stage that is selected from a larger number of embryos. Historically, physicians had a tendency to transfer more embryos to compensate for a low implantation rate. However, with multiple improvements over time, such as optimized embryo culture and stimulation protocols, implantation rates have improved and the practice of transferring multiple embryos was revisited. The rationale was that single ET is really the only effective way to minimize multiple pregnancy rates. Over the last decade, there has been a trend toward a lower number of transferred embryos, with an increase in single ET numbers—this has resulted in a drastic reduction of HOM pregnancy rates.

Worldwide, there is a great variation in the use of eSET. In America, the rate of eSET is about 10% and in Europe about 20% with a wide regional variation (e.g., Sweden, 69%; Finland, 50%; Denmark, 33%). This range can be explained by health care system differences, variability in insurance coverage for IVF, legal factors, local guidelines, and cultural differences. In Sweden, where there is a high rate of eSET because of legal/insurance/cultural factors, one of the largest studies on eSET was performed and published in the *New England Journal of Medicine* in 2004.[156] Six hundred sixty-one patients with a favorable prognosis either had a transfer of two embryos at once or a transfer of one embryo from a fresh cycle followed by a transfer of a thawed embryo if the fresh cycle did not work. At the end of the study, a similar number of women were pregnant in each group; 43% in the group with the double embryo transfer (DET) were pregnant versus 39% in the single ET group. However, the rate of multifetal pregnancy was only 0.8% in the eSET group versus 33.1% in the other group. These results were confirmed in other studies, some of which were prospective randomized trials, and others that were retrospective, including the observation of decreased multiple pregnancy rates after the introduction of eSET programs in some practices.[157–160]

Probably, the most striking difference in multiple pregnancy rates was observed in a study from Colorado published in *Fertility and Sterility* in 2004.[161] In this study, 48 good prognosis patients were randomized to receive either one or two embryos at the blastocyst stage, when the embryologist had monitored the embryos for a longer period of time, with an opportunity to select the very best embryos. The pregnancy rate in the DET group was 76% compared to a pregnancy rate of 61% in the eSET group. However, almost half of the patients in the DET group had twins (47%), whereas none of the patients in the eSET group did (0%).

All these observations have led to a lively debate about the topic of eSET. Given that multiple pregnancies, with the resulting consequences of increased health issues in mothers and newborns, clearly represent a burden to society and health care systems, experts have pushed for increased use of eSET in patients with a good prognosis, summarized by one author in an editorial on this topic: "Replace as many embryos as you like, one at a time."[162]

Challenges to more universal acceptance of eSET are potential increases in cost for the patient, limitations of our methods to select the best embryos, and in some places, the capacity to freeze extra embryos. Clinics may also be worried about their statistics because "success rates" are reported per cycle and not per patient. Efforts to decrease the multiple pregnancy rates may also not be valued enough by patients because of a lack of awareness of multiple pregnancy risks in the general public. Ultimately, evidence-based education for providers and patients and a thorough counseling discussion between the couple and their IVF doctor are crucial, so that the desired end result of pregnancy is achieved in as many patients as possible, while maximizing the chances of a healthy outcome for the mother and her infant.

RECURRENT PREGNANCY LOSS

The traditional definition of recurrent pregnancy loss (RPL) is the occurrence of three or more consecutive losses of clinically recognized pregnancies prior to the 20th week of gestation. Biochemical, ectopic, and molar pregnancies are not included. The ASRM defines RPL as two or more failed pregnancies (documented by ultrasound or histopathologic examination).[1]

A limited assessment is recommended after each loss and a thorough evaluation after three or more losses. RPL can be primary or secondary—primary if it occurs without an antecedent live birth and secondary if it occurs after a prior live birth was achieved. RPL is a very emotionally distressing condition to affected couples. It is often a frustrating condition to treat because the etiology remains unknown in approximately half of investigated cases,[163] and currently, no definitively effective evidence-based treatment options for unexplained RPL exist.

Epidemiology of Recurrent Pregnancy Loss

Of all recognized human pregnancies, approximately 15% will end in spontaneous abortion. The actual incidence of spontaneous pregnancy loss is greater when early, unconfirmed pregnancies are included. In one study, daily urine specimens from 221 healthy women attempting to conceive were analyzed using ultrasensitive hCG assays. The total rate of pregnancy loss after implantation was 31%.[164] These estimates do not include instances where fertilized oocytes fail to implant. Approximately 1% of all women trying to conceive have recurrent miscarriage, defined as three previous

miscarriages; when recurrent miscarriage is defined as two previous miscarriages, the proportion rises to 5%.[165] Statistically, if a miscarriage frequency of 15% is assumed, then the probability of three consecutive miscarriages would be (0.15)*(0.15)*(0.15), or 0.003 (0.3%). The actually observed frequency of RPL is slightly higher than that (approximately 0.5 to 1%).

Etiology of Recurrent Pregnancy Loss

The mere presence of an etiologic factor does not signify that it is the definitive cause of recurrent miscarriage. Determination and initiation of appropriate therapy should be based only on the expectation that eradication of identified risk factors will enhance the likelihood of a subsequent live birth.

Genetic Factors

Available data suggest that the incidence of abnormalities of fetal chromosome number or structure in first-trimester sporadic or isolated spontaneous abortions exceeds 50%. It appears that the incidence of chromosomal abnormalities in patients with RPL is not significantly different from the one in patients with sporadic pregnancy loss.[166,167] Approximately 30% of second-trimester abortions and 3% of stillbirths demonstrate abnormal karyotypes. The vast majority of these are due to errors in gametogenesis (chromosomal nondisjunction during meiosis), fertilization (triploidy), or the first division of the fertilized ovum (tetraploidy or mosaicism). Only about 5% are due to structural abnormalities such as translocation.[168,169]

In terms of the distribution of aneuploidy in first-trimester losses, autosomal trisomy (of chromosomes 13, 16, 18, 21, and 22) is the most common abnormal karyotype (50%), followed by monosomy X (20%), triploidy (15%), tetraploidy (10%), and structural abnormalities (5%).[170] Trisomy is the addition of an extra chromosome to a haploid set of chromosomes, or $2n + 1$, whereas triploidy is when three full haploid sets of chromosomes—or $3n$—are present in all cells. The most common monosomy is 45 XO (Turner syndrome). The incidence of aneuploidy increases with age, reaching rates of over 70% in karyotype analyses of fetal tissue in a cohort of 180 women older than age 35 years.[171] In approximately 2 to 4% of couples with RPL, one partner will have a genetically balanced structural chromosome rearrangement.[172] Karyotypic abnormalities consist of balanced translocations in the majority of cases and less commonly of chromosome inversions. Balanced translocations can cause pregnancy loss because segregation during meiosis results in gametes with duplication or deficiency of chromosome segments. Translocation and inversion are associated with a higher risk of pregnancy wastage and are indications for prenatal diagnosis or PGD in subsequent pregnancy.[173,174] Practitioners often test for more common causes for RPL first and proceed with genetic analysis if the initial testing reveals no abnormality. In order to determine which couples to refer for karyotypic analysis, it is also helpful to know which patient factors increase the likelihood of abnormal paternal karyotype as the etiology: maternal age at second miscarriage, a history of three or more miscarriages, a history of two or more miscarriages in a brother or sister of either partner, and a history of two or more miscarriages in the parents of either partner.[175]

In patients with RPL and normal maternal and paternal karyotype, the role of preimplantation genetic screening (PGS) is controversial. PGS, also referred to as preimplantation genetic diagnosis, is used with IVF to avoid transfer and implantation of an affected embryo. PGS does improve the pregnancy outcome of translocation carriers with a history of RPL.[176] If it is done only for advanced maternal age, however, it is associated with a reduction in the live birth rate.[177] A systematic review of the available literature revealed five observational studies reporting live birth rates between 19 and 46% (mean 35%, median 40%) and miscarriage rates between 0 and 10% (mean 9%, median 9%).[178] Of note, all of the reviewed studies used fluorescence in situ hybridization (FISH) technology with a panel of up to seven probes. Newer techniques for PGS such as quantitative polymerase chain reaction (qPCR) and array comparative genomic hybridization (CGH) are increasingly used—their use in this context is currently being studied.

Structural/Anatomic Anomalies

Structural abnormalities in the reproductive tract, such as Müllerian anomalies (most commonly a uterine septum), Asherman syndrome, or uterine fibroids, are present in 10 to 25% of patients with RPL, compared to 5% in the general population.[179] These can be evaluated by pelvic ultrasound, magnetic resonance imaging (MRI), sonohysterography, HSG or hysteroscopy. There are no randomized trials looking at pregnancy outcomes after uterine surgery done for RPL, although there are some studies that support the efficacy of this approach.[180,181] The most common uterine anomaly, the uterine septum, is thought to impair vascular flow in the endometrium. Therefore, its removal is thought to decrease miscarriage rates,[182] although no high-quality prospective evidence for this hypothesis is available. The situation is similar for uterine fibroids and polyps—their removal is recommended, but solid evidence that it decreases miscarriage rates is lacking.[75,183]

Endocrine Causes

Overt uncontrolled thyroid disease, whether hypo- or hyperthyroidism, increases the rate of miscarriage. In addition, recent evidence suggests that even in patients with subclinical hypothyroidism, the risk of

miscarriage increases when the TSH is greater than 2.5 or if the patient has thyroid antibodies (serum thyroid peroxidase antibody). Women with increased serum thyroid peroxidase antibodies have a high risk of developing hypothyroidism in the first trimester and autoimmune thyroiditis postpartum, so they need to be monitored appropriately. There is some evidence that for these women (even if they are currently euthyroid), use of thyroid hormone during pregnancy may decrease the risk of spontaneous abortion and preterm birth.[184,185] However, these findings need to be confirmed in larger prospective trials. Currently, there is no recommendation for universal TSH screening in the first trimester. In patients with a history of RPL, however, thyroid testing should be undertaken.

Uncontrolled diabetes mellitus is a risk factor for pregnancy loss, although good diabetic control can restore miscarriage rates to those of nondiabetic women.[186] Screening for the presence of diabetes is indicated in the workup of RPL. Diabetic patients who desire pregnancy should have their hemoglobin A_{1C} levels optimized before they attempt conception.

Elevated serum prolactin concentrations are thought to play a role in RPL,[187] and attempts should be made to normalize values in RPL patients and any patient attempting to conceive.

Women with PCOS have a higher pregnancy loss rate than women without PCOS. Metformin has been used to decrease this risk, but its effectiveness to do so is unproven.

Whether a "luteal phase defect" and the serum progesterone concentrations play a role in the etiology of RPL is a matter of debate. Therefore, it is currently unclear whether a midluteal progesterone value should be obtained in patients with RPL and what prognostic indications different values of progesterone in the midluteal phase have.

Immunologic and Hematologic Factors

The successful outcome of pregnancy depends on the development of adequate placental circulation. Patients with antiphospholipid antibodies (lupus anticoagulants and anticardiolipin antibodies) are at increased risk for venous and arterial thrombosis, resulting in an increased rate of spontaneous abortion and/or intrauterine fetal death. Antiphospholipid antibody syndrome is diagnosed with the following criteria:[188]

Persistent positivity in tests for lupus anticoagulant and/or anticardiolipin antibody *plus* one of the following:

- Three or more consecutive spontaneous losses before week 10 of gestation
- One or more premature births (before 34 weeks) due to severe pre-eclampsia or impaired fetal growth
- One or more unexplained intrauterine deaths beyond 10 weeks' gestation

Overall, antiphospholipid antibodies are present in 10 to 15% of patients with RPL; anticardiolipin antibodies are more common than lupus anticoagulants. In patients with antiphospholipid antibodies, the fetal loss rate approaches 70%.[189]

It is well established that in women with recurrent miscarriage and a diagnosis of the antiphospholipid syndrome, treatment with aspirin and heparin improves pregnancy outcomes, even if some inconsistencies exist in the results from available randomized trials.[190–192]

Many investigators hypothesized that there was an association between RPL and the presence of inherited thrombophilias such as activated protein C resistance, antithrombin III deficiency, hyperhomocysteinemia, and factor V Leiden (heterozygote and homozygote). Available evidence is inconclusive as to whether these conditions are associated with RPL and whether anticoagulant treatment in these conditions decreases pregnancy loss rates in RPL patients.

Multiple immunologic factors have been implicated in the etiology of RPL. The role of natural killer cells has been extensively investigated, but it is currently unclear whether testing should be recommended to identify which RPL patients may potentially benefit from immune therapy.[193] There is no evidence to support any benefit from the use of immunotherapy or glucocorticoids for the treatment of RPL.[194–196]

Other Factors

Various other etiologies have been proposed for RPL. There is currently no concrete evidence that infectious agents are a major cause of RPL. Environmental factors have been implicated—smoking, for example, is a documented risk factor; in one study, women who smoked more than 14 cigarettes per day had a 1.7 relative risk for spontaneous abortion.[197] Toxic environmental influences such as tobacco and alcohol should be avoided in pregnant patients with and without RPL, given their teratogenic effects.

Idiopathic/Unexplained Recurrent Pregnancy Loss

Based on earlier discussion, patients with RPL should have a workup to assess the most common causes, including structural, endocrine, and genetic testing. If, however, the workup is negative, which is the case in a large proportion of patients, multiple treatment approaches have been investigated.

Given that anticoagulant therapy has a positive effect in RPL patients with a diagnosis of the antiphospholipid syndrome, treatment with aspirin and heparin was attempted empirically in patients with idiopathic RPL. In the Anticoagulants for Living Fetuses study, a multicenter, randomized, placebo-controlled trial, low-dose aspirin combined with low-molecular-weight heparin or aspirin alone, as compared with placebo, did not

improve the live-birth rate among women with unexplained recurrent miscarriage.[198]

Similar results were observed with other experimental therapies for unexplained RPL such as corticosteroids or intravenous immunoglobulin. It is also currently unclear whether RPL patients benefit from ART such as IVF.

Progesterone is commonly prescribed for RPL, but large, randomized trials demonstrating its efficacy for this are lacking. Some studies have demonstrated benefit but the numbers of women with RPL in these trials is small, and more rigorous methodology needs to be improved in designing future trials to evaluate this use of progesterone.[199,200]

Therefore, many practitioners advocate sympathetic and frequent counseling for patients in which an abnormality cannot be identified[201] until new proven therapies are discovered. Ultimately, a high number of patients with RPL will achieve a live birth with supportive treatment alone, even after multiple prior losses.[170]

CLINICAL NOTES

- Infertility is the inability to conceive after 12 or more months of regular intercourse without contraception and affects approximately 10% of couples trying to conceive a child.
- Fecundity (f) represents the probability of conception per month of effort and is calculated by dividing the number of conceptions (C) by the person-months of exposure (T): $f = C/T$.
- Assuming a 20% monthly probability of pregnancy among normally fertile couples, the cumulative probability of pregnancy after 12 months is 93%.
- Overall, about half of all infertile couples will seek treatment, although only 25% will obtain assistance from an infertility specialist.
- Assessment prior to a year of infertility is warranted in women who have a history of oligomenorrhea/amenorrhea, are older than age 35 years, and have known or suspected pelvic pathology.
- Initial tests for couples with infertility include semen analysis, menstrual history, assessment of urinary LH surge prior to ovulation and/or luteal phase serum progesterone level, hysterosalpingography, and day 3 serum FSH and estradiol levels.
- Additional testing of infertility may include pelvic ultrasound, laparoscopy, further tests for ovarian reserve, and thyroid function testing.
- Ovarian reserve testing initially is done with day 3 serum FSH and estradiol levels but may also involve a clomiphene citrate challenge test, ultrasound for early follicular antral follicle count, day 3 serum inhibin B level, or anti-Müllerian hormone measurement.
- Ovulatory dysfunction and anovulation affect 15 to 25% of all infertile couples seeking therapy.
- The most common causes of ovulatory dysfunction are PCOS, thyroid dysfunction, hyperprolactinemia, and late-onset congenital adrenal hyperplasia.
- Ovarian reserve testing should be done prior to starting treatment for oligo- or anovulation.
- The WHO has classified anovulation into three main groups: Group I is hypogonadotropic hypogonadism or hypothalamic amenorrhea; Group II is eugonadotropic ovulatory dysfunction; Group III is hypergonadotropic hypoestrogenic anovulation.
- The majority of patients in the WHO II category have PCOS.
- AMH levels above 0.5 ng/mL are thought to represent a good oocyte reserve, whereas those less than 0.15 ng/mL are indicative of a poor response to IVF if the woman's oocytes are used.
- Approximately 40% of all infertile women will demonstrate an abnormality of the uterus, cervix, and/or fallopian tubes.
- The most common etiology for tubal disease causing infertility is PID, most often secondary to genital infection with *C. trachomatis*.
- Male factor infertility is the only cause of infertility in approximately 30% of couples and a contributing factor in another 20 to 30%.
- If a man's semen analysis is abnormal, it should be repeated after at least 1 month by a laboratory that adheres to WHO guidelines, with a quality control program ensuring accurate testing.
- In men with azoospermia and severe oligospermia (less than 5 to 10 million sperm/mL), associated genetic abnormalities may be present.
- The three most common genetic abnormalities associated with azoospermia and severe oligospermia are (a) CF gene mutations associated with CBAVD, (b) chromosomal abnormalities resulting in impaired testicular function, and (c) Y-chromosome microdeletions associated with isolated spermatogenic impairment.
- Varicoceles are found in 15% of normal men and in approximately 40% of men presenting with infertility.
- The main steps of the IVF process are ovarian downregulation, ovarian stimulation, oocyte aspiration, and ET.

(continues)

- RPL is the occurrence of three or more consecutive losses of clinically recognized pregnancies prior to the 20th week of gestation.
- Of all recognized human pregnancies, approximately 15% will end in spontaneous abortion. The actual incidence of spontaneous pregnancy loss is greater when early, unconfirmed pregnancies are included.
- The incidence of chromosomal abnormalities in patients with RPL is not significantly different from the one in patients with sporadic pregnancy loss.
- Structural abnormalities in the reproductive tract are present in 10 to 25% of patients with RPL, compared to 5% in the general population.

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CHAPTER 12

Early Pregnancy Failure and Ectopic Pregnancy

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Early pregnancy failure (EPF), also referred to as miscarriage or abortion, is the most common complication of early pregnancy.[1] Almost one in four women will experience EPF in her lifetime. Costs associated with the management of EPF within the United States in 2002 were estimated at more than 260 million dollars.[2] With the improvement in ultrasound technology, the nomenclature and diagnosis of EPF has greatly improved.

Ectopic pregnancy (EctP) diagnosis and treatment has also improved over the last several decades. This is likely due to the improvement in the sensitivity of serum beta human chorionic gonadotropin (beta-hCG) assays, contribution of high-resolution ultrasound, and the rise in the use of laparoscopy and medical methods for treatment.[3] Improved technology has likely contributed to the complacency fostered with the diagnosis and treatment of EctP, but the EctP still remains a major source of morbidity and mortality for reproductive age women and is the third most common cause of pregnancy-related death.[4]

The ultrasound has been instrumental in more accurately distinguishing between EPF and EctP. The goal is to shape our understanding of these two common early pregnancy complications and provide a framework for how to recognize them.

TERMINOLOGY

The terminology of EPF, depending on where you are in the world, is likely to be different.[5] Many terms are used in the literature to describe the failure of a pregnancy in early gestation, which can lead to confusion in patient counseling.

The term abortion likely originates from 15th century Latin "*aboriri*" meaning "to disappear, perish or pass away, be lost, or miscarry."[6] Originally intended to reflect both spontaneous and intentional acts, there arose a distinction between intentional and spontaneous abortion likely in the late 19th century. The term miscarriage came to be used in reference to a spontaneous event, whereas leaving the original term, abortion, associated with an intentional act. Currently, the American College of Obstetrics and Gynecology favors the World Health Organization definition of abortion, "expulsion or extraction of an embryo or fetus weighing 500 g or less from its mother."[7]

The term *early pregnancy failure* refers to either an embryonic/fetal demise or anembryonic pregnancy.[8] The broader lay term ***miscarriage*** encompasses EPF, inevitable and incomplete abortion, and any fetal loss until viability is reached.

An **embryo** encompasses a human offspring in the early stages following conception and implantation and up to the end of the eighth week of life.[9] Studies that refer to a loss prior to 10 weeks' gestation should refer to the loss as an embryonic loss rather than a fetal loss. A **fetus** is a developing human from usually 2 months after conception to birth.[9] A loss after the 10th week of gestation should reference as fetal loss.

With the advent of ultrasound to make the diagnosis of pregnancy and EPF, older terminology based on physical exam findings is sometimes not helpful. The term **missed abortion**, where the uterus has somehow "missed" recognizing the abortion is of little help clinically. This term originated when physical exam findings did not correlate with menstrual recall, and the size of the pregnancy on physical exam was less than that expected by gestational age. **Incomplete and inevitable abortions** also have their origins in physical exam findings. Incomplete abortion refers to incomplete passage of embryonic/fetal tissue, whereas inevitable abortion describes a process in place that cannot be stopped. These terms have more to do with a physiologic process rather than an underlying cause.[8]

Early pregnancy loss (EPL) is another term sometimes used to describe the early failure of a pregnancy. EPL more specifically refers to pregnancy losses that occur before clinical recognition, so-called hidden events.[10] These are conceptions that occur and fail before implantation. The patient likely would not have known she had become pregnant and passed the pregnancy at the time of her normal menses. With the development of more sensitive assays, these events have been elucidated.

INCIDENCE

EPF is the most common complication of early pregnancy. In those women with clinically recognized pregnancies, 8 to 22% will experience EPL.[11] When all conceptions are taken into account, including EPL, the rate of

EPF is greater than 30%,[12] a rather inefficient process. This information is useful when treating and counseling patients because it may help to allay the anxiety that is experienced by a patient undergoing miscarriage. The percentage of patients undergoing miscarriage decreases as gestational age increases,[13] with about 80% occurring within the first 12 weeks.[14] Miscarriage after 15 weeks in genetically normal fetuses is unusual.[13] This trend in decreasing incidence with increasing gestational age is important as we discuss the risk factors and etiology for EPF.

RISK FACTORS

There have been numerous studies directed at uncovering the most common risk factors for EPF. To date, the most compelling reasons are advancing maternal age and a history of pregnancy loss.[15,16]

In a case control study, which took place in the United Kingdom, the rate of miscarriage was 75% higher in women older than the age of 35 years, increasing to a five-fold risk of fetal loss after the age of 40 years.[16] A study of the Danish Medical Birth Registry, including more than a million women that were admitted to the hospital, discovered the same trend with almost half of the women at age 40 years and older undergoing early miscarriage.[15] This association between maternal age and miscarriage is depicted in Figure 12.1. Logically, this increase in maternal age–associated miscarriage can be explained by a woman's older genetic material, but even when chromosomal abnormalities are taken into account, maternal age is an independent risk factor for miscarriage.[17]

Previous EPL is also a strong predictor of future miscarriage, with the odds increasing with each subsequent EPL,[16] reaching a greater than three-fold increase with three prior losses. In this study, a history of a previous live birth decreased miscarriage rates by as much as 40% in subsequent pregnancies. These investigators also noted a doubling of the miscarriage rate in those women that had taken longer than 12 months to conceive compared to those who had conceived within 3 months and a higher rate of miscarriage in those women that were not married or in a stable relationship.

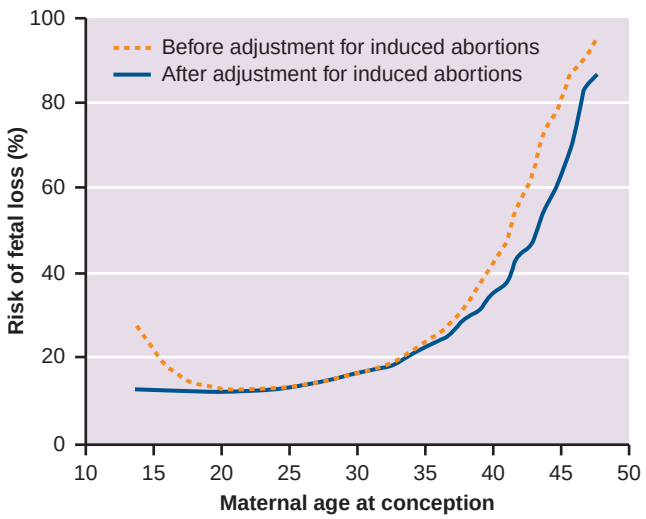

FIGURE 12.1 Risk of fetal loss from spontaneous abortion, ectopic pregnancy, and stillbirth according to maternal age at conception.

Smoking has been linked to EPL. In a large case control study, Ness et al.[18] showed an increase in the rate of miscarriage among women with positive urine cotinine (cigarette breakdown product) and positive self-report history of smoking as compared to controls. George et al.[19] found a similar association among smoking and miscarriage, even reporting a link between environmental tobacco smoke (ETS) and miscarriage. In this study, they also analyzed the chromosomes of the products submitted. The association between ETS and miscarriage did not exist among miscarriage products that had a normal chromosomal analysis. Maconochie et al.[16] did not find an association between smoking and miscarriage. Other risk factors that have been associated with an increased risk of miscarriage include alcohol intake, cocaine use, and maternal weight.[18,20] A recent meta-analysis of overweight and obese women compared to controls noted an almost two-fold increase in the risk of miscarriage among the former.[21]

Endocrine causes such as diabetes and thyroid abnormalities have been linked with an increased risk of miscarriage.[22,23] Infectious etiologies have not been rigorously studied to determine if they play a role in miscarriage.

Autoimmune factors have received much attention lately in regard to miscarriage. Acquired thrombophilias such as the lupus anticoagulant and anticardiolipin antibodies have been linked with second- and third-trimester losses.[23] It remains to be seen whether this holds true within the first trimester and whether testing and treatment in those with recurrent miscarriage benefit from addressing these factors. Inherited thrombophilias including protein C, S, and G20210A have also received attention as a cause of miscarriage, but the data surrounding this is confusing, conflicting, and costly if put into practice. Currently, there is a need for additional prospective data to make recommendations in regard to screening and treatment of these disorders.

Lastly, anatomic factors such as uterine fibroids and uterine anomalies may play a role in miscarriage, but more prospective data on these relationships is needed.[24]

ETIOLOGY

The great majority of EPFs are due to chromosomal abnormalities or congenital anomalies not compatible with life. Congenital anomalies are usually due to an underlying genetic cause with some secondary to environmental factors (teratogens).[23] Other causes of EPF are those associated with the patient such as an underlying anatomic abnormality (intrauterine septum or submucosal fibroid) or a poorly controlled endocrinopathy (diabetes, thyroid disease).[23,24] Often, the explanation for miscarriage in a patient that has undergone recurrent losses cannot be determined.

Cytogenetic abnormalities are found in 50% of EPF specimens. The earlier the gestational age at which miscarriage occurs, the higher the incidence of chromosomal abnormality discovered. Abnormal karyotype may be present in as much as 90% of anembryonic pregnancies, decreasing to 50% at 8 to 11 weeks' gestation and 30% by 16 to 19 weeks' gestation.[25] By far, the most common cytogenetic cause is autosomal trisomy (60%), followed by monosomy X (20%), and triploidy (20%).[26] As pregnancy advances, the chromosomal abnormalities discovered are similar to the abnormalities seen in live born infants: trisomy 21, 18, and 13.[27]

CLINICAL FEATURES AND DIAGNOSIS

Women that are possibly undergoing miscarriage present with irregular bleeding and sometimes uterine cramping. These women may or may not know that they are pregnant. A urine pregnancy test is necessary for all women of childbearing age that present with unexplained vaginal bleeding. In those that are pregnant, a quantitative serum beta-hCG test and/or ultrasound can aid in determining the cause. An algorithm for approaching these patients is detailed in Figure 12.2.

If the woman is not pregnant, management should be based on the history and physical exam findings. If she is pregnant and appears to be in the process of aborting with products passed or at the cervical os, management should be undertaken to complete the process. An **incomplete abortion** may be confirmed on physical exam with discovering products of conception or even the patient bringing tissue or relating a story of passing tissue at home, and the presence of other physical findings such as an open cervical os, continued vaginal

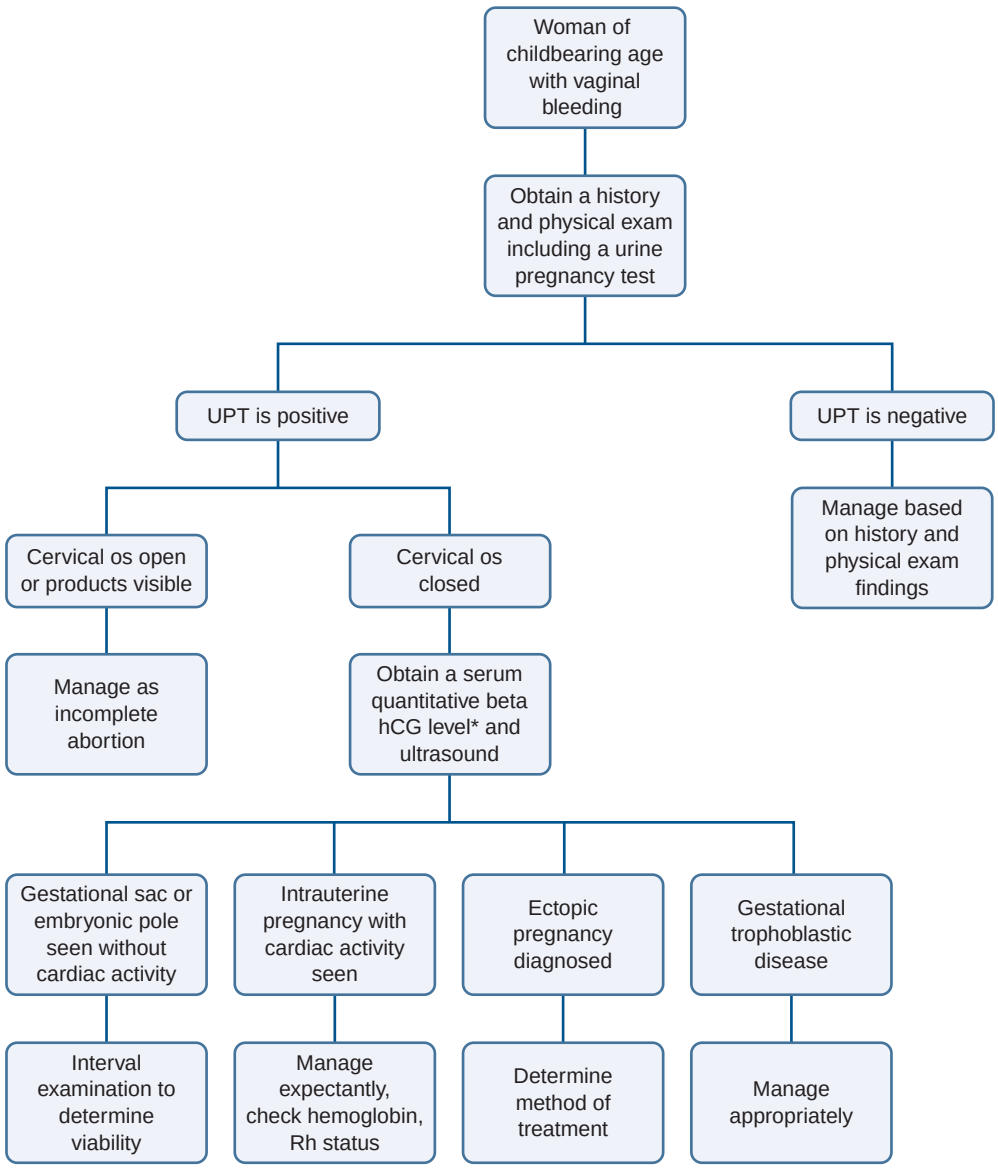

FIGURE 12.2 Algorithm for vaginal bleeding. Serum beta-hCG level should be above your institution's threshold for ultrasonographic visualization. UPT, urine pregnancy test.

bleeding, and cramping. The cramping associated with the miscarriage process should cease once the products are no longer in the uterus. **Inevitable abortion** refers to bleeding of intrauterine origin and progressive cervical dilation without passage of tissue.

If she is pregnant, with vaginal bleeding, a closed os, ultrasound evidence of intrauterine contents, and without history or evidence of passing tissue, the scenario is referred to as a **threatened abortion**. The serum beta-hCG level and ultrasound are crucial to determine whether the pregnancy is viable, failed, ectopic, or gestational trophoblastic disease.

The **gestational sac** is the first intrauterine structure seen on ultrasound in pregnancy. This can be visualized around 4 weeks and is usually 2 to 3 mm in size. Visualization of the gestational sac allows one to determine if a pregnancy is within the uterine cavity, eliminating the possibility of EctP except in the rare case of a **heterotopic** pregnancy where there exists pregnancies in two implantation sites. A heterotopic pregnancy is encountered rarely[28] unless assisted reproductive techniques are employed where the incidence is higher.[29]

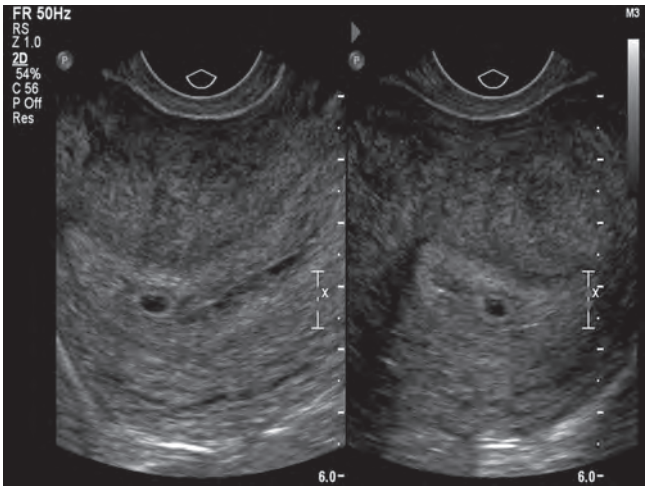

FIGURE 12.4 Pseudogestational sac.

The gestational sac is visualized as an anechoic space (clear) surrounded by a hypoechoic rim (bright echoes). The sac is *eccentric* in its intrauterine location and spherical in shape (Fig. 12.3), which should be distinguished from the centrally located "pseudogestational sac" (Fig. 12.4).

The first structure seen within the gestational sac is the **yolk sac**. The yolk sac can be visualized by the fifth week of gestation. The yolk sac provides nourishment to the developing embryo and is a round sonolucent structure with a bright rim (Fig. 12.5). Thickening of the margin of the yolk sac is referred to as the **fetal or embryonic pole**. The fetal pole is the embryo in its somite stage. A better term would be embryonic pole, but fetal pole is often used. Between 5 and 6 weeks' gestation, fetal cardiac activity should be present within the embryonic pole.

Recent ultrasound studies classify fetal demise (again the nomenclature is confusing and embryonic demise

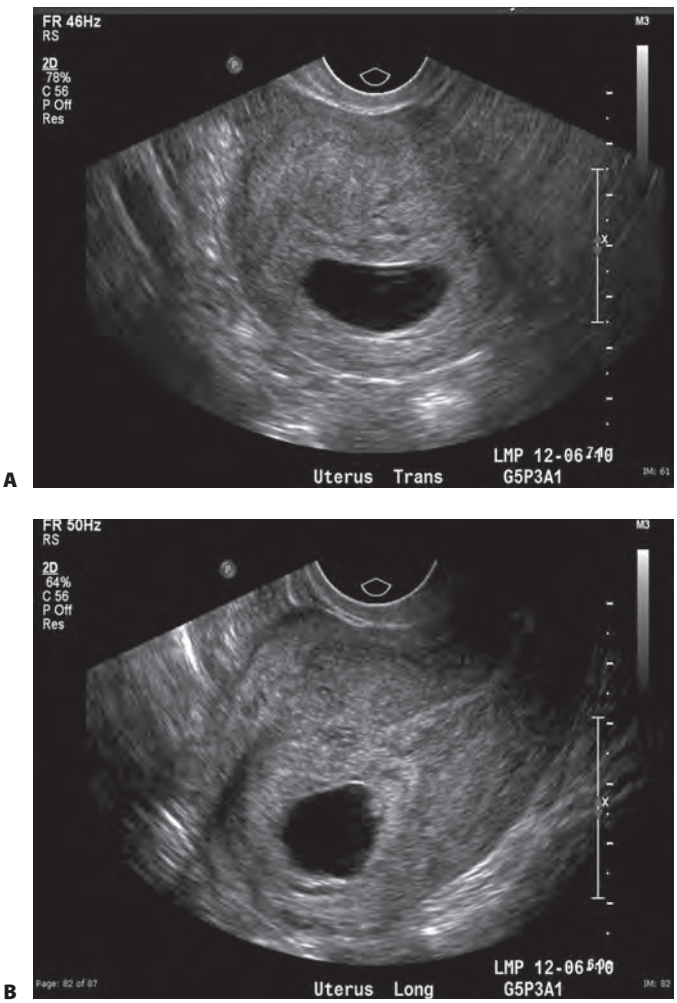

FIGURE 12.3 Gestational sac. **(A)**: Uterus trans. **(B)**: Uterus long.

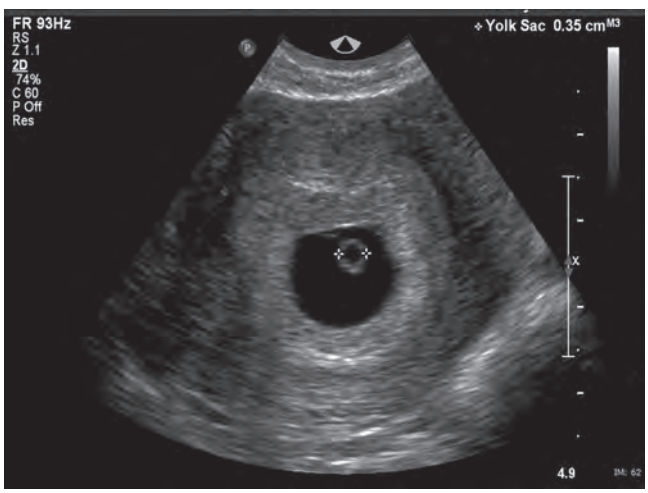

FIGURE 12.5 Yolk sac.

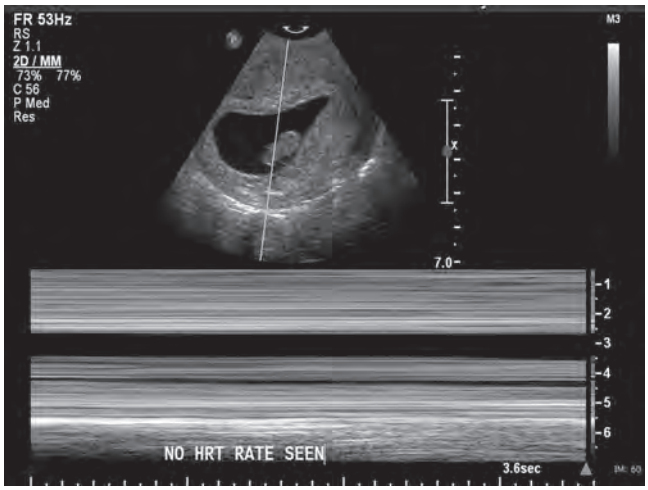

FIGURE 12.6 Embryonic or fetal demise.

would be more correct) once the fetal pole measures 5 mm without the presence of cardiac activity.[30] In this scenario (Fig. 12.6), the embryonic disk develops, but no further discernible development is noted.[8] Fetal or embryonic demise can replace the oft-used term missed abortion, which continues to linger although adds little useful clinical information.[31]

Anembryonic pregnancy is an empty gestational sac measuring more than 15 or 20 mm in diameter without a fetal pole or the lack of interval growth in a smaller gestational sac on repeat sonogram after 7 days.[32] In this situation, the embryonic disk does not develop or has resorbed after the trophoblast has invaded the decidual lining of the uterus[8] (Fig. 12.7). Anembryonic pregnancy can replace **blighted ovum**, which was used to describe an empty gestational sac with no embryo.

A combination of physical exam skills, laboratory data, and ultrasound can be used to determine whether a pregnancy is a miscarriage, viable intrauterine pregnancy, or ectopic. Urine pregnancy tests are qualitative with a minimum detection level of 20 to 25 mIU/mL. Serum tests can be either, but when trying to determine viability of a pregnancy, the quantitative test is most helpful, and the minimum detection level is 1 to 5 mIU/mL. Hospital laboratories use different references and measures, making comparisons between two different sites problematic. For this reason, it is not recommended to compare quantitative beta-hCG levels between two different laboratories.

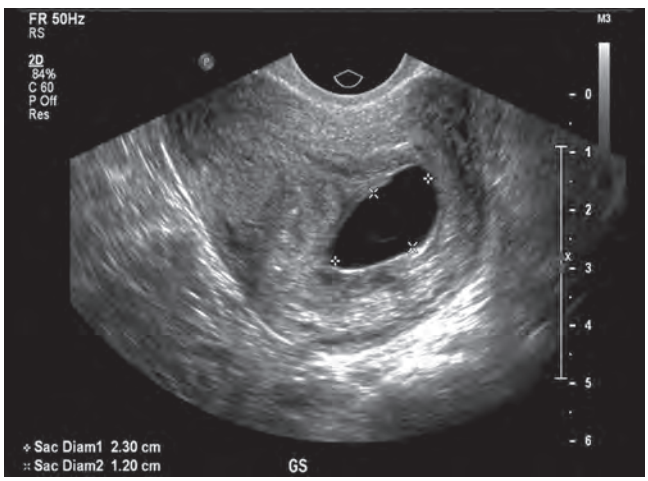

FIGURE 12.7 Anembryonic pregnancy.

The beta-hCG level at which an intrauterine pregnancy should be seen on ultrasound varies based on the experience of the sonographer, position and density of the uterus, presence of fibroids, obesity, and multiple pregnancy.[33] Women who present with a beta level above a certain value, termed the discriminatory human chorionic gonadotropin (hCG) zone,[34] and no evidence of an intrauterine pregnancy on ultrasound are considered to have an ectopic.

The beta-hCG level in pregnancy rises in a curvilinear fashion until 41 days of gestation,[35] with 85% of viable pregnancies showing at least a 66% increase in beta level over a 48-hour period.[36] For a viable pregnancy, the slowest recorded rise of beta-hCG during this early time period is 53% over a 48-hour interval.[37] From this point, it rises more slowly until it peaks at around 100,000 IU/L (range of 27,000 to 230,000 IU/L) at approximately 8 to 11 weeks' gestation.[38] After the peak, it decreases reaching a stable point at approximately 12,000 IU/L (range of 2000 to 50,000 IU/L) at 24 weeks. Differentiating between the miscarriage and EctP can sometimes be a challenge.

False positive beta-hCG tests can occur and can have untoward outcomes for the patient if not recognized, exposing them to unnecessary tests and treatments, sometimes even hysterectomy.[39] The false-positive test does not occur that often, likely 1 in 10,000 to 1 in 100,000 tests.[40] The false-positive test can be attributed to a number of factors. Most often, large heterophilic antibodies can create a false-positive result. If a false-positive test is suspected and the quantitative value of the test is above the minimum threshold for a urine pregnancy test, then a urine pregnancy test should be ordered to confirm a positive test. The antibodies that are likely causing a false-positive test are larger than the hCG molecule and are usually not filtered through the kidney. If the urine pregnancy test is negative, nothing further is warranted. If the test is less than the urinary threshold, for example, greater than 5 mIU/mL but less than 25 mIU/mL, then serial dilutions of the serum sample should be undertaken in order to document a parallel decrease in the value. When diluting the sample with a buffer of equal volume, the beta-hCG value should be 50% less than the original sample.[41] A value greater than or less than a 50% decrease confirms the diagnosis of a false-positive beta-hCG level.

ECTOPIC PREGNANCY

Implantation of the developing blastocyst outside the endometrium of the uterine cavity results in an EctP. Most ectopic pregnancies, 98%, occur within the fallopian tube,[42] and the following discussion focuses on the tubal ectopic.

Incidence/Terminology

Approximately 2% of all pregnancies in the United States are ectopic,[43] although the incidence of EctP is difficult to ascertain in the United States recently due to the number of patients increasingly treated as an outpatient.[44] Also, calculations of incidence are hampered by the number of EPLs that are missed, decreasing the denominator in the calculation, and likely leading to an overestimation. In the United Kingdom, this number is about 10 cases per 1000 pregnancies and has remained stable.[45] The most recently released Centers for Disease Control and Prevention (CDC) data within the United States is 20 per 1000 pregnancies.[4] The cost of inpatient treatment of EctP in the United States has been estimated at 1.1 billion in the year 1992.[46]

Most ectopic pregnancies occur in the fallopian tube, the ampullary region being the most common location followed by the isthmus and fimbria.[47] Figure 12.8 shows these anatomic locations on the fallopian tube. For those that occur outside the tube, the following is a list in descending order of their incidence: ovary, interstitia, abdomen, and cervix.

An **interstitial pregnancy**, sometimes referred to as a cornual pregnancy, technically occurs in the fallopian tube. Implantation that occurs along the proximal tube that lies within the myometrium of the uterus is an interstitial pregnancy.[48] It is usually not classified as a tubal pregnancy because of the location and difficulty that arises when attempting treatment. Historically, a **cornual pregnancy** is an ectopic that occurs within a horn of a bicornuate uterus, rudimentary horn of a unicornuate uterus, or the lateral half of a septated uterus.[49] Another rare but distinct entity is the **angular pregnancy**. This intrauterine pregnancy occurs in the uterine angle, medial to the uterotubal junction, and can be confused with interstitial pregnancies. The angular pregnancy can be distinguished from the interstitial pregnancy exteriorly because it displaces the round ligament superiorly and laterally, whereas the latter produces an enlargement lateral to the round ligament.[50] The **abdominal pregnancy** is believed to occur most commonly after a tubal or ovarian abortion implants in the peritoneal cavity or direct implantation on a peritoneal surface.[51] The **cervical pregnancy** occurs after implantation takes place within the endocervical canal.

Risk Factors

There are numerous risk factors for EctP and a detailed history should include questions accounting for them, although up to half of all women with an EctP have no identifiable risk factors.[52] Among pregnant women

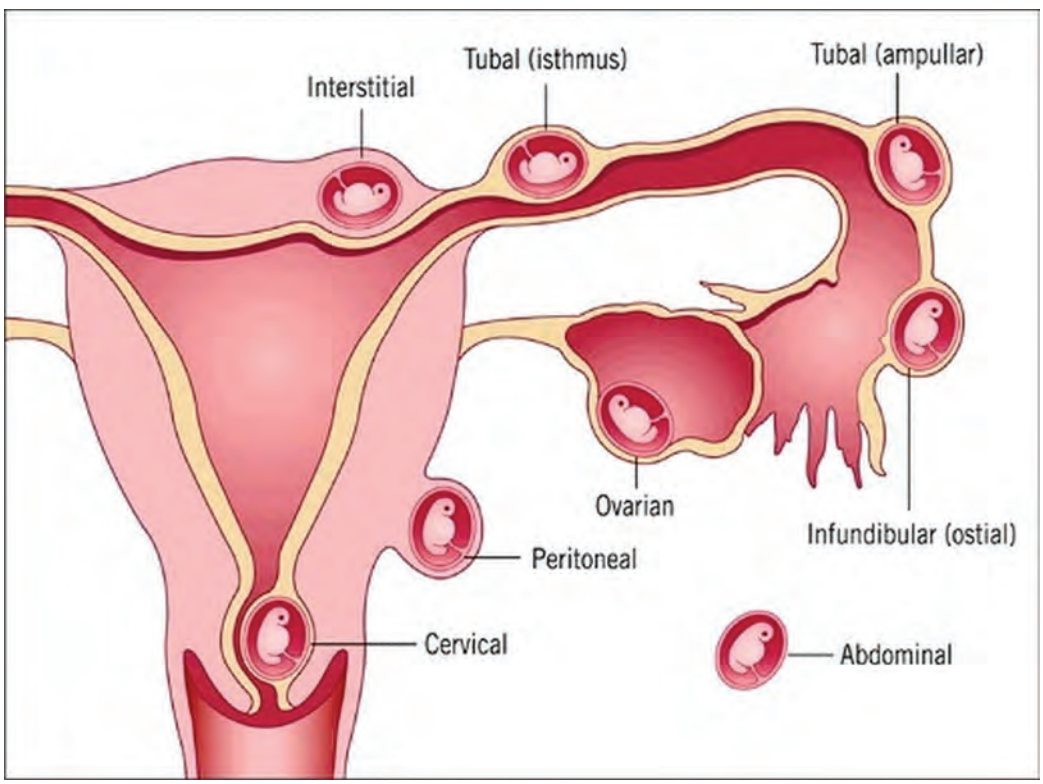

FIGURE 12.8 Anatomic locations on the fallopian tube. (From Seeber BE, Barnhart KT. Suspected ectopic pregnancy. *Obstet Gynecol*. 2006;107[2, pt 1]:399–413.)

who present to the emergency center within the first trimester with complaints of bleeding, pain, or both, the prevalence of ectopic ranges from 6 to 16%.[53]

Because the location of the ectopic is most commonly in the fallopian tube, risk factors for its development revolve around damage to the tube whether by prior surgery, infection, or other factors that alter tubal motility and function.[54] Prior EctP, prior tubal surgery, and tubal sterilization remain the greatest risk factors for developing an EctP.[46] Regardless of treatment method for an ectopic, medical, or surgical means, the likelihood of a subsequent ectopic is high.[55] In women with prior tubal surgery for infertility, the tubal surgery itself predisposes to an increased risk of future ectopic, but the indication for the original tubal surgery carries the greater risk.

Prior tubal sterilization, the most effective form of birth control, carries a risk of failure around 1%. Bipolar coagulation used at the time of tubal sterilization has been classically associated with the highest failure rates.[56] In patients who become pregnant with prior tubal sterilization, 15 to 33% are ectopic in location.[57]

Prior sexually transmitted infections increase the risk of ectopic, thus women with multiple sexual partners and those who begin to have sexual intercourse at an earlier age are at greater risk. Smoking, history of infertility, and increasing maternal age also play a role.[43] In utero, diethylstilbestrol (DES) exposure has been linked with EctP.[58] In women that use contraception, the risk of pregnancy is low, but if these women conceive, their risk of ectopic compared to controls is higher.[59]

Etiology

There are likely either factors present in the embryo that lead to premature implantation or tubal factors that cause a delay in fertilization or transport into the uterine cavity. Unlike the miscarriage, where chromosomal abnormalities are the leading cause, analysis of EctP chorionic villi shows similar genetic composition to normal pregnancies.[60–62]

The most common etiology of EctP is infection leading to tubal damage resulting in a chronic salpingitis. In a comparison of tubal pathology between patients with ectopic and controls, chronic salpingitis was noted to be more common among those with ectopic.[63] They also noted a large number of cases of salpingitis isthmica nodosa, a disease of unknown etiology leading to hypertrophy of the muscular layer of the tube.

Clinical Features and Diagnosis

Women who present with EctP classically are said to present with abdominal pain, amenorrhea, and irregular vaginal bleeding.[64] Culdocentesis was the diagnostic method used in the past[65] and now is rarely used to diagnose EctP due to the improvement in ultrasound technology. Also, the previously mentioned symptoms are identical to the patient who presents with threatened miscarriage, which is far more common. These symptoms combined with peritoneal signs, suggesting tubal rupture or bleeding into the peritoneal cavity, are different altogether, and appropriate measures should be taken when a patient presents in such manner.

A careful history, including questions in regard to risk factors, and physical exam is crucial in attempting to determine the difference between these two clinical entities but cannot be the sole means used to do so. Women presenting with clinical signs and symptoms mentioned earlier must include the diagnosis of an ectopic in their differential. Not including ectopic in the differential can lead to increased morbidity and even maternal death.

With the development of ultrasound and the use of this modality early in pregnancy to determine gestational age, the diagnosis of EctP has shifted to an earlier gestational age. As mentioned before, women who present with a beta level above the discriminatory zone[37] and no evidence of an intrauterine pregnancy on ultrasound are considered to have an ectopic. Although with the improvement in ultrasound technology, the concept of the discriminatory zone has been challenged.[65]

Initially, the discriminatory zone was described using transabdominal ultrasound. Transabdominal ultrasound visualization of an empty uterus and a beta level of greater than 6500 IU/L[66] were considered above the discriminatory zone, suggestive of an EctP, and an indication for laparoscopy. Use of transabdominal ultrasound requires the presence of a full bladder, is time consuming, and adds little to transvaginal ultrasound results. Transvaginal ultrasound is also well tolerated by patients and should be the first imaging modality employed.

Transvaginal ultrasound can identify intrauterine contents earlier in gestation than transabdominal ultrasound, lowering the discriminatory zone. This value is reported in the literature anywhere from 1000 IU/L to 2000 IU/L, with many sites using 1500 IU/L. This value varies based on the institutional and radiologic experience with transvaginal ultrasound in detecting ectopic pregnancies. There should be some discussion with your institutions' radiology department in regard to setting a discriminatory zone. Using a lower beta value as the discriminatory zone (1000 IU/L) increases the sensitivity of detecting EctP but has poor specificity, increasing the likelihood of interrupting a normal pregnancy. Using a higher discriminatory zone (2000 IU/L) has the advantage of decreasing the number of false positives but also increases the delay in treatment of an ectopic, possibly leading to increased morbidity.

Given that serum progesterone levels are higher in a normal intrauterine pregnancy versus an abnormal pregnancy (miscarriage or ectopic), some have tried to use the serum progesterone level as an ancillary marker in order to diagnose an EctP. A meta-analysis of the topic revealed that a progesterone level less than 5 ng/mL

was diagnostic of an abnormal pregnancy but failed to differentiate between a miscarriage and ectopic.[67] A prospective series suggested that a progesterone level greater than 22 ng/mL reliably excluded the diagnosis of EctP but was limited due to its observational nature, low prevalence of EctP in their patient population, and the exclusion of asymptomatic patients that presented to the emergency center.[68] At our institution, we do not routinely employ the progesterone level to diagnose/exclude the EctP.

In the evaluation of an EctP, a single beta level, regardless of its relation to the discriminatory zone, is not sensitive enough to provide definitive determination of an ectopic. Therefore, a repeat beta level, usually within 48 to 72 hours, and evaluation are necessary to diagnose the EctP. *Exceptions to this rule* include the clinical suspicion of a ruptured ectopic or ultrasound visualization of an empty uterus and any of the following seen on ultrasound: extrauterine gestational sac with cardiac activity, extrauterine gestational sac with fetal pole and no cardiac activity, adnexal mass with a hyperechoic ring around a gestational sac, and an adnexal mass separate from the ovary.[68] Signs of a ruptured ectopic include pain, peritoneal signs, and even signs of hypovolemic shock. The patient with a positive beta level that presents with abdominal pain, peritoneal signs, and evidence of free peritoneal fluid should be considered an ectopic and surgery is justified. Delay in treatment can only lead to increased morbidity.

As mentioned earlier, the 99% rate of rise in a beta level in a normal early pregnancy should be at least 53% over a 48-hour period.[37] Thus, a beta level rate of rise over 48 hours less than this is an abnormal pregnancy 99% of the time. *Therefore, in the patient without clinical suspicion of an ectopic, a beta level below the discriminatory zone, and an empty uterus or no demonstration of an ectopic, a repeat beta level in 48 to 72 hours to look for an appropriate rise is warranted.*

For the patient that demonstrates an appropriate 48-hour beta level rise (greater than 53%) but without documentation of an intrauterine pregnancy, the possibility of ectopic is not excluded; as many as 21% of ectopic pregnancies will demonstrate this rise.[68] These patients (greater increase than 53% over 48 hours without a documented intrauterine pregnancy) need to be followed with repeat imaging in order to document the location of the pregnancy. Figure 12.9 highlights the change in hCG concentration in the intrauterine pregnancy, EctP, and miscarriage.[67]

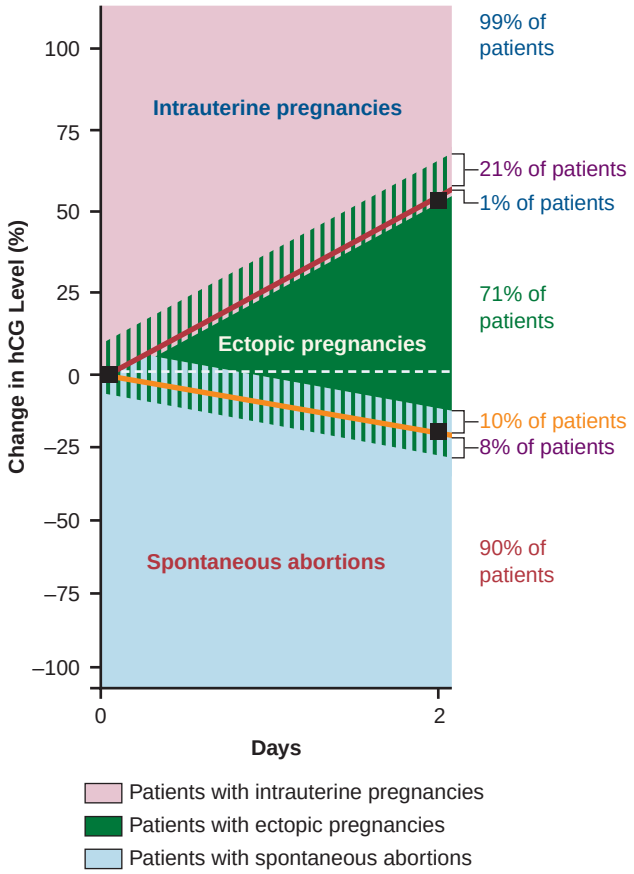

FIGURE 12.9 The change in hCG concentration in the intrauterine pregnancy, ectopic pregnancy, and miscarriage. (From Barnhardt KT. Clinical practice. Ectopic pregnancy. *NEJM*. 2009;361[4]:379–387.)

Treatment

EctP can be treated in the office with methotrexate in a safe and less expensive way that could preserve future fertility.[69] The ideal candidate is a patient with confirmed EctP who is hemodynamically stable, able to follow up, and with easy access to an emergency room.[70]

Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase, resulting in a block in the synthesis of thymidine and inhibition of DNA synthesis. Methotrexate has been used for the treatment of malignancy, rheumatic disorders, psoriasis, and termination of intrauterine and now EctP.[71] Methotrexate affects all the fast-dividing tissues, including gastrointestinal (GI) system, bone marrow, and epithelium, is excreted by the kidney, and is hepatotoxic. It is advisable to obtain transaminases and creatinine before the administration of methotrexate and not use it in people with blood dyscrasias or active GI or respiratory disease.[71,72] If medical management is an option, a very detailed informed consent should be obtained, making sure the patient understands the risk of the methotrexate use and her compromise to follow up at the schedule times[70] (Table 12.1).

Treatment Protocols

There are three protocols described in the literature: single-dose, two-dose, and a multiple-dose protocol.[73] The most commonly used protocol is the single-dose protocol because it is the simplest, and failure rate for methotrexate single-dose protocol is 3.7% if beta-hCG is less than 5000 mIU/mL; when the beta-hCG is greater or there is cardiac activity, it is advisable to use the multiple-dose

TABLE 12.1 Contraindications

Absolute

- Breast-feeding
- Overt or laboratory evidence of immunodeficiency
- Alcoholism, alcoholic liver disease, or other chronic liver diseases
- Pre-existent blood dyscrasias (bone marrow hypoplasia, leukopenia, thrombocytopenia, or severe anemia)
- Known sensitivity to methotrexate
- Active pulmonary disease
- Peptic ulcer disease
- Hepatic, renal, or hematologic dysfunction

Relative

- Embryonic cardiac motion
- Gestational sac larger than 3.5 cm

From American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 94: Medical management of ectopic pregnancy. *Obstet Gynecol.* 2008;111(6):1479–1485.

TABLE 12.2 Single-Dose Protocol

Day 1	Beta-hCG, transaminases, creatinine, CBC, type and screen, methotrexate
Day 4	Beta-hCG
Day 7	Beta-hCG

Beta-hCG, beta human chorionic gonadotropin; CBC, complete blood count.

protocol. This chapter describes in detail the single-dose protocol because it is the most common one used.[70]

Before starting any protocol, it is advisable to obtain kidney and liver function test in case patients will need a second dose or you decide to use the multiple-dose protocol.[73]

The single dose consist of a 50 mg/m^2 single injection of methotrexate following a beta-hCG day 4 and a beta-hCG day 7, expecting a decrease greater than 15% between day 4 and 7 (Table 12.2).[74] If the beta-hCG decrease is greater than 15%, serial weekly beta-hCG need to be obtained until the beta is undetectable to the nonpregnant level.[71,74]

If there is less than 15% decline in the beta-hCG between days 4 and 7, repeat dose of methotrexate. If this is the case, the follow-up with beta-hCG will continue counting the day of the second dose of methotrexate as day 1.[74]

If it is more than 15% decline between days 4 and 7, follow titers weekly until negative beta-hCG.

Patient must be informed of the potential complications such as rupture; side effects; and avoidance of alcohol, folic acid supplements, nonsteroidal anti-inflammatory drugs (NSAIDs), sexual intercourse, strenuous physical activity, and sun exposure.[70,75] Side effects most commonly mentioned are excessive flatulence, bloating, nausea, vomiting, stomatitis, diarrhea, and elevated liver function tests.[74] Rare but severe side effects include nephrotoxicity, interstitial pneumonitis, and alopecia dermatitis. Side effects can be limited by dose and length of treatment.[73]

Complications

Abdominal pain known as separation pain is common after medical management with methotrexate; the causes are unknown and could be a tubal abortion or stretching from the tube after hematoma formation.[76] Pain can be controlled with NSAIDs that have showed better control than narcotic analgesics.[73] There is association between use of NSAIDs and decrease of methotrexate excretion, but this seems to be minimal with the low dose used for ectopic.[77]

Patients need to be advised to call the office or go to the emergency room if the abdominal pain does not resolve after few hours of usual use of analgesics. Those patients with abdominal pain might require in-hospital observation, but surgery is not required unless they become unstable.[76]

Medical management with methotrexate is a viable and safe option to treat ectopic pregnancies. It is the decision of the physician to incorporate methotrexate into his or her practice.

CLINICAL NOTES

- EPF is the most common complication of early pregnancy.
- The terminology used to describe miscarriage could be standardized, which would improve patient communication and recording of accurate statistics worldwide.
- An **embryo** encompasses a human offspring in the early stages following conception and implantation up to the end of the eighth week or 10 weeks' gestation.
- A **fetus** is a developing human from usually 2 months after conception to birth.
- Advancing maternal age and previous miscarriage are well-established risk factors for miscarriage.
- **Anembryonic pregnancy** is an empty gestational sac measuring more than 15 or 20 mm in diameter without a fetal pole or the lack of interval growth in a smaller gestational sac on repeat sonogram after 7 days.
- A fetal demise is diagnosed if the fetal pole within the gestational sac measures 5 mm without the presence of cardiac activity.
- Anembryonic pregnancy should replace the oft-used term blighted ovum.

(continues)

- Fetal or embryonic demise should replace the term missed abortion.
- The EctP is common, representing 2% of all pregnancies in the United States, most of which are located within the fallopian tube.
- The biggest risk factor for ectopic is prior tubal infection, although most women diagnosed with EctP have no risk factors.
- Transvaginal ultrasound is the imaging modality of choice when attempting to differentiate a normal pregnancy from an abnormal pregnancy.
- A 48-hour repeat quantitative beta-hCG value is necessary to diagnose an EctP, except in cases of a suspected ruptured ectopic or if definitive signs of an ectopic are visualized on transvaginal ultrasound.
- Treatment options are surgical, expectant, or medical management.
- Medical management is with methotrexate, a chemotherapeutic agent.
- The single-dose protocol is the most common protocol used.
- Indications of medical management is a patient hemodynamically stable, able to follow up, and with easy access to an emergency room.
- Adverse effects are pretty rare, and the side effects are well tolerated.

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CHAPTER 13

Surgical and Medical Abortion

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INTRODUCTION

Providing safe abortion services is a very important contribution to women's health. Induced abortion is a major cause of maternal mortality in countries where abortion access is restricted. The countries with the highest rates of unsafe abortion are in Africa and Latin America, and the highest death rates from unsafe abortion are in East Africa, about 160 per 100,000 live births.[1] Unsafe abortion was once a major contributor to maternal mortality in the United States as well. In the 1940s, there were more than 1000 abortion-related deaths per year in the United States. Now with abortion legalized, there are only a few abortion-related maternal deaths each year. The U.S. abortion-related mortality rate in 1997 (the last year with complete data) was 0.6 deaths per 100,000 abortions. Risk of maternal death increases with gestational age. According to data from the Centers for Disease Control and Prevention (CDC), at gestational ages less than 8 weeks, the rate of maternal death is 1 per 1,000,000 legal abortions.[2] More than 60% of U.S. abortions occur in the period of 8 weeks or less when the risk of complications or death is the least.[3] The CDC estimates that 87% of the abortion-related deaths that occur in the United States could have been prevented had the women been able to obtain abortion services by 8 weeks.[2]

The provision of safe abortion services is neither difficult nor expensive but requires the political will to put maternal safety ahead of tradition and dogma. Safe services are readily provided in an office or health center setting. In early pregnancy, only simple and inexpensive instruments are needed, and in the United States and other countries where mifepristone and misoprostol can be obtained, medication abortion provides another highly effective and safe method without surgery in most cases.

According to the most recent data available from the Guttmacher Institute,[4] almost half of all pregnancies in the United States are unintended, and nearly a quarter of these pregnancies end in abortion. In 2005, there were 1.2 million abortions performed in the United States, 8% fewer than in 2000.[5] Thirty-seven percent of abortions occur in Black women, 34% in non-Hispanic white women, 22% in Hispanic women, and 8% in other races. Furthermore, the abortion rate in women living below the federal poverty level is more than four times that of women above 300% of the poverty level. Abortion access is limited geographically. Eighty-seven percent of U.S. counties have no abortion providers[6] and one-fourth of women have to travel more than 50 miles to reach a provider.[7]

Similarly, access may be hampered by restrictions and lack of insurance coverage of abortion. Access is even more of a problem as gestational age advances. Nearly 90% of abortions happen in the first 12 weeks of pregnancy, 3.5% occur between 16 and 20 weeks, and only 1.1% at greater than 20 weeks' gestation. Although most abortion providers offer services to 8 weeks, the number of providers decreases with advancing gestational age. Sixty-seven percent of providers offer some second-trimester services, whereas only 20% of providers offer services after 20 weeks. The majority of providers are ob-gyn physicians. A National Abortion Federation (NAF) survey in 2002 reported that 77% of the male providers and 38% of the female providers were ob-gyn physicians.[5] Forty-four percent of female providers are family practice physicians. The population of abortion providers is also getting older. The majority of male providers in the NAF survey were older than 55 years of age. Younger providers were more likely to be female. Abortion services are provided in a wide variety of clinical settings. One-third of providers work in hospitals, one-fifth in private physician offices, and the remainder of providers work in free-standing clinics.[6]

Counseling and Informed Consent

According to an American College of Obstetricians and Gynecologists (ACOG) committee opinion in 2009, all health care providers must provide patients with accurate and unbiased information and refer patients to other providers in a timely manner if they are unable to themselves provide the requested services.[8] Similarly, women presenting with an unintended pregnancy must be presented with accurate and unbiased information regarding her options. Table 13.1 suggests the components to be discussed with the patient.[9]

Equally important in preprocedural counseling is an assessment of the mental health of the patient. As former Surgeon General C. Everett Koop testified before Congress, the development of significant psychological

TABLE 13.1 Elements of Informed Consent for Induced Abortion

- The gestational age of the pregnancy
- All available options including adoption, parenting, and termination
- Potential benefits and risks of continuing the pregnancy and termination
- The voluntary nature of the patient's decision
- The abortion procedure appropriate to her pregnancy duration
- Advantages and complications of each method
- Available anesthesia options and their benefits and risks
- Tests that may be performed to diagnose or treat the patient's condition
- Any ancillary tests or procedures
- Permission to treat the patient in the event of a complication or emergency
- If the patient is a minor and if required by law, obtaining permission from the parent or court prior to her abortion care
- Her understanding of the required forms

From Baker A, Beresford BA. Informed consent, patient education and counseling. In: Paul ME, Lichtenberg ES, Borgatta L, et al, eds. *Management of Unintended and Abnormal Pregnancy: Comprehensive Abortion Care*. Oxford, UK: Wiley-Blackwell; 2009:50, with permission.

problems related to abortion is "miniscule from a public health perspective."[10] Although poor psychological outcomes postabortion are uncommon, especially in those obtaining first-trimester abortions, women who may be at increased risk of such outcomes should be identified during preprocedural counseling and should be followed appropriately both during and after the procedure.[10] This includes women who lack social support for their abortion, who have more conflicting feelings regarding their decision, those terminating a highly desired pregnancy, and those with pre-existing psychological conditions, which may make it difficult for them to cope with life's stresses. The counselor should attempt to assess the patient's current social, financial, and cultural situation; the patient's understanding of her alternatives; any pressure she perceives on her decision-making process; her expectations of her feelings of her decision in the future; any history impacting her current decision; the circumstances surrounding the pregnancy; and her understanding of the impact her decision will have on her future and current situation.[11] A patient who remains undecided at the completion of her counseling session can be referred to other services (e.g., high-risk obstetrics, social worker, clergyman) if appropriate and offered an additional counseling session if she remains ambivalent.

Preprocedural Evaluation

A complete gynecologic and obstetric history should be elicited including a history of cervical conization, cesarean sections, uterine duplication anomalies, a history of bleeding during the current pregnancy, or a history of ectopic pregnancy. Any coexisting medical conditions should also be screened for and treated appropriately. The remainder of the preoperative evaluation should consist of a hematocrit or hemoglobin and testing for Rh status.

The majority of surgical abortions occur in free-standing clinics. There are very few contraindications to a clinic or office procedure. Serious pre-existing medical conditions such as severe cardiovascular or pulmonary disease are best managed in a hospital setting. Patients with suspected placenta accreta, second-trimester molar pregnancies, and cervical pregnancy are at high risk for hemorrhage. Patients with poorly controlled seizure disorders, poorly controlled hypertension, severe asthma, and coagulation disorders are also best managed in the hospital where this is possible. A conversation with the patient's primary care physician may allow for advance treatment that will allow safe abortion to be provided in the office setting with follow-up by her primary physician. Unfortunately, in some communities, hospitals and physicians refuse to accept patients needing abortion regardless of their medical condition.

In the United States, ultrasound has become an increasingly important part of abortion care. An accurate preprocedure assessment of gestational age is important. Although the 2002 NAF survey found that 91% of abortion providers confirm pregnancy with an ultrasound, the remainder of providers perform a pelvic examination for dating, using ultrasound only when a discrepancy arises.[5] Other clinical indications for an ultrasound include symptoms or a history of ectopic pregnancy, inability to perform a pelvic exam, and pregnancies suspected to be less than 6 weeks. In a study of patients in a South African clinic, women's estimates of pregnancy duration averaged 19 days less than the gestational ages estimated by ultrasound.[12] The providers' clinical estimates were somewhat more accurate. Half were within 1 week of the ultrasound estimate and three-quarters were within 2 weeks.

Basic ultrasound machines are usually sufficient for pregnancy dating. A vaginal probe 5 to 10 MHz allows for visualization of early pregnancies, assessment of the adnexa in cases of suspected ectopic, and evaluation of the endometrium if retained tissue or clot is suspected. Abdominal probes of 3 to 5 MHz are sufficient to confirm intrauterine pregnancies in many women over 7 weeks.

Typically, a gestational sac is the first ultrasonographic sign of pregnancy. A normal sac will be symmetrical, eccentrically located in the uterus, and have the appearance of an echogenic ring with a sonolucent center. The discriminatory human chorionic gonadotropin (hCG) level at which a sac can be seen transabdominally is approximately 3600 mIU/mL, and transvaginally, that level is approximately 1500 to 2000 mIU/mL, although these numbers can vary in the presence of fibroids, multiple gestations, maternal obesity, prior uterine surgery, or uterine position.[13,14] Fossum et al.[15] reported the presence of a gestational sac at 34.8 ± 2.2 days from last menstrual period or an hCG of 1398 ± 155 using transvaginal ultrasound. A fetal pole was detected at 40.3 ± 3.4 days or an hCG 5113 ± 298. To distinguish a pseudogestational sac from a true intrauterine gestational sac, a yolk

sac should be present. Typically, a yolk sac should be seen with a transvaginal probe if the mean gestational sac diameter has reached 13 mm.

Special Considerations

Abnormal placentation should be suspected in patients with a history of a prior cesarean section and evidence of a low-lying placenta or a previa on ultrasound. Given the increase in the number of cesarean sections performed, this is expected to be an increasingly common occurrence in abortion care. Reported rates of accreta in second-trimester dilatation and evacuation (D&E) are 0.04%.[16] If accreta is suspected prior to a procedure, a formal ultrasound should be obtained. Ultrasound has an excellent negative predictive value and a moderately good positive predictive value in identifying accreta. In cases of an unclear ultrasound or with a posterior placenta, a magnetic resonance imaging (MRI) may also be useful.[17] In cases of accreta suspected before an abortion is initiated and when there is no desire for future fertility, a planned hysterectomy may be the most appropriate option. In addition, a history of prior cesarean sections may also complicate a procedure if the uterus is adherent and fixed to the bladder. Ultrasound guidance may help complete a procedure under these circumstances.

In patients with known cervical or uterine anomalies, the appropriate medical or surgical procedure should be chosen based on the extent of the anomaly. Medical abortion may often be the safest option in eligible patients.

Antibiotics

The use of prophylactic antibiotics is routine with surgical abortion in the United States and is recommended by the ACOG.[18] An extensive meta-analysis of randomized controlled trials in 1996 concluded that antibiotics were beneficial even in women in low-risk categories. An overall 42% decrease in the risk of infection was demonstrated.[19] Generally, doxycycline is recommended because of its broad spectrum of antimicrobial coverage, oral absorption, and low cost.[18] A common regimen is to give 200 mg of doxycycline by mouth with food immediately before or after the procedure.

Whether all or some patients requesting abortion should be screened for chlamydia and gonorrhea is a separate issue. The incidence of chlamydia in an abortion population is high, ranging from 7 to 20%.[5] A review published in the *British Journal of Obstetrics and Gynaecology* concluded that the more cost-effective approach to preventing postabortal infection is universal antibiotic prophylaxis but that this approach would not prevent the long-term morbidity associated with chlamydia.[20] The benefits of routine testing are multiple: (a) to provide complete treatment with doxycycline for patients testing positive for chlamydia; (b) to identify patients with gonorrhea, an organism frequently resistant to tetracyclines; (c) to treat or allow identification of partners at risk. The disadvantage of screening is added cost. The appropriate strategy may depend on the local rate of gonorrhea and chlamydia and the availability of resources.

Choice of Procedure

Both medical and aspiration abortion are highly effective and safe. Women express different reasons for preferring one procedure over. Some women feel that a medical abortion is less invasive, provides them with more control, offers more privacy, and allows them to avoid a surgical procedure. Other women choose a surgical procedure because they want a quick, more predictable procedure and may want anesthesia. In a study published in the *British Medical Journal*, 363 women less than 9 weeks were assigned to either randomization or their choice of abortion method. Twenty percent of the women presenting for an abortion had a preference for medical abortion, 26% preferred a vacuum aspiration, and the remainder were willing to undergo either method. Of women given their choice of procedure, only 4% of women would choose the other method next time. However, in those women randomly assigned to either medical or surgical abortion, 2% of the surgical abortion patients would choose medical next time, whereas 22% of the medical patients would prefer a surgical procedure with their next abortion.[21] This suggests that choice is an important factor in a woman's satisfaction but that having experienced medical abortion, the surgical approach seems preferable to some.

SURGICAL ABORTION

Uterine aspiration (also called vacuum curettage or suction curettage) was introduced into the United States during the late 1960s and is by far the most common method of abortion in the United States. Procedures before 13 menstrual weeks are by convention, suction or vacuum curettage. Those procedures after 13 weeks are called dilatation and evacuation.[22]

Pain Relief for Office Abortion

Naproxen sodium 550 mg taken 1 to 2 hours prior to the procedure has been found to reduce peak pain scores during abortion as well as to decrease postabortion pain.[23] This or other nonsteroidal anti-inflammatory drugs (NSAIDs) given preoperatively have become part of routine practice.[24]

There is great variability in the type of pain relief offered with abortion services, but paracervical block with local anesthetics is the mainstay. In the latest NAF survey from 2002, 46% of first-trimester providers use local cervical anesthesia with or without oral premedication, one-third use local anesthesia combined with intravenous (IV) sedation, and 21% use deep sedation or general anesthesia.[5]

Despite paracervical block, many women report significant pain with their procedure. In a large study, 34% of patients undergoing first-trimester uterine aspiration reported pain that was "severe" or "very severe."[25] After decades of reliance on paracervical block, there is conflicting evidence as to whether it works at all. A 2006 randomized trial of lidocaine versus bacteriostatic saline in paracervical block found no difference in pain relief.[26] A recent systematic review found two additional randomized trials comparing paracervical block to no treatment or to bacteriostatic saline.[27] The first study found no difference in pain scores with dilatation, aspiration, or postoperatively; however, both groups also received IV conscious sedation.[28] In the second study, the group receiving the active agent (1% chloroprocaine) did have better pain control, but the mean improvement in pain scores was only 1 point on an 11-point scale, probably too little to be clinically significant.[29] One group of investigators has reported that adding 30 mg of ketorolac to 18 mL of 1% lidocaine provided greater pain relief than oral ibuprofen and a plain lidocaine paracervical block.[30] In a new approach, an intrauterine infusion of 5 mL of 4% lidocaine via a 3 mm Novak cannula 3 minutes prior to vacuum abortion reduced procedural pain significantly when compared to paracervical block alone. Lidocaine serum levels were measured and were well below the toxic range.[31] This is a promising technique, which should be studied further.

Several authors have studied variations in technique for paracervical anesthesia for abortion.[32] Injecting 10 to 20 mL of 1% lidocaine deep (1 to 1.5″) into the cervical stroma is more effective than superficial injections beneath the cervical mucosa.[33] Deep injections at 12, 4, and 8 avoid the lateral cervical vessels while providing as adequate analgesia as multiple injections at 12, 3, 4, 8, and 9.[29] In comparison with plain lidocaine, buffering lidocaine to a neutral pH reduces pain from the injection itself and also has been reported to reduce the pain with dilatation and the pain perceived at the end of procedure.[33] Buffering is accomplished by adding 5 mL of 8.4% sodium bicarbonate solution to 45 mL of 1% lidocaine solution.[34] Furthermore, the addition of 2 to 4 units of vasopressin has been reported to reduce blood loss from the procedure and may help prevent postabortal atony.[35]

Increasingly, practitioners offer IV conscious sedation. Allen and colleagues[36] compared oral oxycodone and sublingual lorazepam to IV sedation with 100 mcg of fentanyl and 2 mg of midazolam in a randomized controlled trial. Pain relief was much better for the group who received the IV sedation. Older trials using lower doses of fentanyl 50 to 100 mcg found statistically significant decreases in pain when compared to placebo, but the women still reported less than adequate pain relief with their procedure.[37] One milligram of oral lorazepam by itself is not better than placebo in relief of pain.[38] IV sedation with narcotics and anxiolytic agents adds risk for respiratory arrest and for aspiration of gastric content. Using IV sedation in an office setting requires limiting the dosages to avoid deep sedation, monitoring with continuous pulse oximetry, the availability of oxygen supplementation if needed, and the presence of a trained assistant to observe the patient in addition to the surgeon. Wilson and colleagues[39] report a series of 1433 patients to 18 weeks' gestation sedated for office abortion under conditions as described earlier with 50 to 100 mcg of fentanyl combined with 1 to 2 mg midazolam. There were no adverse events related to the sedation.

Nonpharmacologic methods such as continuous lower abdominal heat, counseling and skilled conversation, positive suggestion, guided imagery, and other relaxations techniques during the procedure may be helpful.[32] Ultimately, the choice of anesthesia should take into account patient and provider preference, available resources, the clinical setting, and the patient's comorbidities.[40]

Cervical Cleansing

Typically, abortion providers cleanse the vagina and cervix before a procedure with either povidone-iodine or chlorhexidine, although some have called into question this routine practice. One group found no difference in the rate of endometritis after vacuum aspiration when using 0.05% chlorhexidine solution versus 0.9% saline solution.[41] Varli et al.[42] looked at vaginal and vulvar cleansing with chlorhexidine versus vulvar cleansing only and found no significant difference between methods. They hypothesize if vaginal cleansing may in fact promote the growth of more pathogenic bacteria by changing the normal flora.[42] Likely more important in reducing the risk of infection is adherence to meticulous surgical technique including a "no-touch technique" where clinicians wearing either sterile or nonsterile gloves avoid touching those portions of instruments entering the uterus, establishment of a sterile field, and avoidance of tissue trauma.

Surgical Setup

Surgical abortion is provided in a variety of clinical settings including operating rooms, outpatient surgical centers, clinics with procedure rooms, and office examination rooms. The typical room should include an exam table with stirrups or knee-holders and adequate lighting. A source of backlighting such as a photographer's light box and a clear dish to view specimens should also be available.[43] Ultrasound is helpful in cases of difficult dilatation, retroverted uteri, suspected retained tissue, the training of new providers, and second-trimester procedures but is not essential.

A sterile instrument tray should be set up in the room with easy access by the provider. A typical tray

TABLE 13.2 Suppliers of Equipment for Surgical Abortion

Name	Address	Website
Berkeley Medevices, Inc.	1330 South 51st St., Richmond, CA 94804	http://berkeleymedevices.com
Cheshire Medical Specialties, Inc.	1608 Sturbridge Ct., Cheshire, CT 06410	www.cheshire-medical.com
CooperSurgical	75 Corporate Dr., Trumbull, CT 06611	www.coopersurgical.com
Gynex Corp.	2789 152nd Ave., NE Redmond, WA 98052	www.gynexcorporation.com
IPAS	300 Market St., Chapel Hill, NC 27516	www.ipas.org
MedGyn	328 North Eisenhower Ln., North Lombard, IL 60148	www.medgyn.com
Thomas Medical	5610 West 82nd St., Indianapolis, IN 46278	https://www.thomasmedical.com

Adapted from Borgatta L, Kattan DR, Stubblefield P. Surgical techniques for first-trimester abortion. The Global Library of Women's Medicine Web site. http://www.glowm.com/section_view/heading/Surgical%20Techniques%20for%20First-Trimester%20Abortion/item/439. Accessed November 24, 2013.

should include a speculum, tenaculum, ring forceps, a set of graduated tapered cervical dilators (Pratt or Denniston), a small metal curette, gauze, a 21- to 25-gauge spinal needle, a 10-mL syringe, and antiseptic solution. Suppliers of instruments useful in abortion care are listed in Table 13.2.[44]

Most providers use single-toothed tenaculum, an Allis or a Bierer vulsellum tenaculum. Tears may occur less often with these latter designs, but there may also be greater slippage with strong traction. Some providers prefer ring forceps especially at later gestational ages or with more bulbous cervices. A ring forceps is also helpful for possible tamponade at a bleeding cervical laceration site and as an adjunct to suction in late first-trimester procedures.[43] Preferred dilators have a gradual taper, such as Pratt dilators. Denniston dilators are a plastic version of the Pratt dilator. They are much less expensive than the metal Pratt dilators and can be steam sterilized. Routine use of a metal curette is becoming increasingly less common after first-trimester abortion practices. However, a metal curette can be helpful to explore the uterine cavity when retained tissue is suspected. They increase in size starting at 1 mm in width. Cannulae come in both rigid and flexible forms. Rigid forms range from 6 to 16 mm in size. Flexible cannulae are sized from 4 to 12 mm.[43]

The choice of manual versus electric suction is dependent on available resources, gestational age of the patient, and provider experience. In the most recent NAF survey, 49% of providers selectively use manual vacuum aspiration (MVA), an increase from 18% in 1997.[5] MVA instruments are simple, easily carried, and require no electricity. There is no electric pump to purchase, maintain, or clean between cases. Goldberg et al.[45] in a retrospective cohort study of 1726 patients concluded that MVA is as effective as aspiration with an electric pump to 10 weeks' gestation with no difference in complication rates. Similarly, a systematic review of 10 trials comparing manual and electric aspiration in the first trimester found evidence that MVA is as effective as electric suction.[46] At gestational ages less than 50 days, there was less blood loss and less pain associated with MVA. However, electric suction resulted in shorter procedure times. After approximately 10 weeks' gestation, the MVA syringe may need to be emptied once or twice to complete the procedure, so many providers will switch to electric suction at this point in gestation. Many providers also prefer MVA because it is quieter than the electric suction machine. In addition to its use in uterine aspiration, MVA is valuable in treating incomplete abortion, confirming an intrauterine pregnancy in cases of suspected ectopic and in managing acute uterine hemorrhage either in an office or emergency room setting.

There are two basic types of manual aspirators. Both are 60 mL plastic syringes modified so that the plunger can be locked in the open position. One type of aspirator (Ipas MVA Plus) has a valve assembly that allows withdrawing the plunger of the syringe to establish a vacuum before inserting the attached cannula into the uterine cavity. The valves are then opened to aspirate. The other (Milex Handyvac Locking Syringe) has no valve, and the plunger is not withdrawn to create a vacuum until after the cannula is attached to the syringe and inserted into the uterus. With both instruments, the plunger locks into place to prevent loss of vacuum during the procedure.[43,44] The Ipas MVA Plus can be steam sterilized. The Milex Handyvac is meant to be disposable. Both accept plastic vacuum cannulas with a 12-mm diameter base.

An electric suction machine consists of an electric vacuum pump connected through plastic hoses to glass or plastic reservoir bottles. A plastic hose connects to a bottle on the machine while the other end attaches to a plastic control handle that receives the vacuum cannula. There are both reusable and single-use hoses.[43]

Suction Aspiration Procedure

A first-trimester abortion procedure typically begins with a patient in lithotomy position. The provider will perform a basic bimanual exam assessing for uterine size and position and the presence of any adnexal masses.

A sterile speculum is inserted into the patient's vagina. A no-touch technique should be employed throughout the procedure. The operator takes care to avoid touching that portion of an instrument that will go inside the cervical canal. Most providers use povidone-iodine or chlorhexidine to cleanse the vagina and cervix. Approximately 2 to 4 mL of buffered local anesthetic with vasopressin is injected at 12 o'clock. A tenaculum is then placed vertically on the cervix, with one branch extending into the cervical canal. Alternatively, the tenaculum can be placed horizontally. It is important to grasp a sufficient amount of cervical stroma to avoid the tenaculum tearing through the cervix when traction is applied. At this point, the remainder of the local anesthetic is administered. The maximum advised lidocaine dose is 4.5 mg/kg or 20 mL of 1% lidocaine for a 50-kg patient. Generally, 10 to 20 mL of 1% lidocaine is used at two sites, 4 o'clock and 10 o'clock, or at multiple sites around the cervix.[22] Cervical dilatation is then performed being careful to maintain no-touch technique and avoid grasping the dilator by its end. Once sufficient dilatation is achieved, the provider can insert an appropriately sized cannula gently to the uterine fundus. Many providers choose a cannula size equal to the gestational age of the pregnancy (i.e., an 8-mm cannula for an 8-week gestation). Pratt dilators are measured in the French system like urinary catheters. The number on the dilator is the circumference in millimeter. Hence, the number of the largest Pratt dilator used should be approximately three times the diameter of the planned cannula size.

Preoperative preparation of the cervix with misoprostol 400 mcg given vaginally, or buccally 3 hours before a procedure produces cervical softening and some dilatation.[47] This treatment may reduce the risk for cervical injury and uterine perforation. However, this is not yet routine practice. The Society for Family Planning clinical guidelines advocate cervical preparation for all patients at 12 to 14 weeks and consideration of routine use in adolescents.[48] The World Health Organization (WHO) recommends cervical preparation for all women younger than age 18 years, nulliparous women greater than 9 weeks gestation, and all women over 12 weeks.[49]

For electric suction, the hose can be attached to the cannula either before or after the cannula is introduced into the uterine cavity. If a manual aspirator is chosen, the technique depends on the type of aspirator available. For the Ipas brand aspirator, the appropriately sized cannula is attached to the device. The vacuum is then created by closing the valves before pulling the plunger out until the arms snap into place, locking the plunger in the open position. At this point, the cannula can be inserted into the uterine cavity. The valves are then released and the uterine contents evacuated. With the Mylex device, the cannula is connected to the syringe and then inserted through the cervix into the uterine cavity. The vacuum is created by pulling the plunger out and then rotating it slightly to lock it in the open position. Evacuation with any of these devices is achieved by rotation of the cannula as well as a gentle forward and backward motion with the syringe until no more tissue enters the cannula and the uterine cavity has a gritty texture. Some providers routinely use a metal curette to confirm that the uterus is empty and then take one final pass with the vacuum cannula.

After the completion of the procedure, the operator should perform a fresh examination of the aspirated tissue, identifying the gestational sac, and from 9 weeks on, identifying fetal parts as well. This provides immediate reassurance that the pregnancy has been evacuated, confirms that the pregnancy was intrauterine in cases of early pregnancy, and may help to decrease the rate of retained products. In addition, abnormalities such as a molar pregnancy can often be suspected and the specimen sent for formal pathologic exam. In order to inspect the uterine contents, the provider places the contents in a fine strainer and rinses them in running water to remove blood. The tissue is then placed in a clear glass dish and examined over a source of backlight in water. A gestational sac appropriate with the patient's gestational age should be identified. The sac will appear transparent with villi that are frondlike. Small embryonic parts can begin to be identified at 9 weeks' gestation. A typical 6-week sac is approximately the size of a dime, a 7-week sac the size of a nickel, and an 8-week sac the size of a quarter[43] (Figs. 13.1 and 13.2).

In situations where tissue does not confirm an intrauterine pregnancy, an ultrasound is performed to evaluate for ongoing pregnancy or signs of an ectopic pregnancy. Alternatively, if no ultrasound is available or if the ultrasound does not confirm an ongoing pregnancy, blood is drawn for a quantitative beta human chorionic gonadotropin level (beta-hCG). The beta-hCG is repeated in 24 to 48 hours.[50] A drop in value of at least 50% by 24 hours is expected if the pregnancy has been evacuated. Patients for whom this latter option is chosen should be instructed about possible ectopic pregnancy and the need to seek emergency care if abdominal pain develops. The aspirated tissue is also sent for formal pathologic exam on an urgent basis.

Postprocedural Care

Patients should be transferred to a recovery area after their procedure where they can be monitored for bleeding, pain, and signs of early complications. Uncomplicated patients are generally monitored for 30 minutes to 1 hour depending on their level of sedation. NSAIDs or low-dose narcotics are usually sufficient for postoperative pain.[51]

Rh-negative unsensitized patients are given Rh-immune globulin before leaving the facility.

Potential Difficulties

Most first-trimester procedures are completed without significant difficulty or morbidity. However, certain

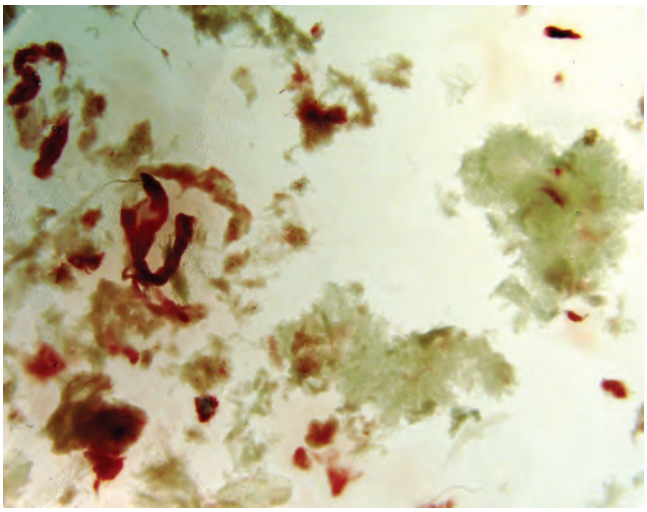


FIGURE 13.1 A 5 3/7 weeks' gestation examined in saline over a photographer's light box.

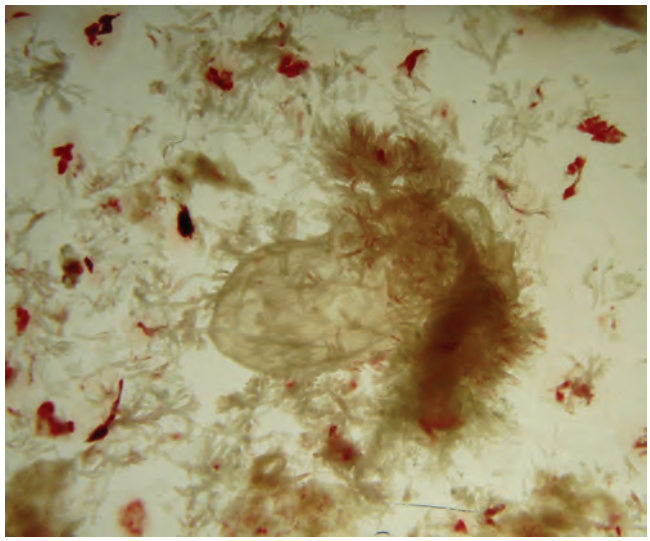


FIGURE 13.2 A 7 3/7 weeks' gestation examined in saline over a photographer's light box.

conditions can increase the difficulty of a procedure. Among these conditions are maternal obesity, cervical stenosis, a fibroid uterus, and severe retroversion or anteversion. Each of these conditions will be discussed separately in the following text.

Obesity is becoming an increasingly common problem in the United States with almost half of all reproductive age women being overweight or obese.[52] Obesity has been associated with longer and more difficult procedures and a greater blood loss.[53] In planning for care of obese patients, consider the weight limit of your gynecologic table, the possible need for assistance for retraction and visualization, and the need for longer surgical instruments and appropriately sized speculum. An assessment of airway status should also be made before committing to in-office sedation. A common problem with very obese women is that the vagina is long and the cervix cannot be easily reached. A very helpful maneuver is to elevate the stirrups vertically toward the ceiling. This produces flexion of the legs on the trunk. If this is not sufficient, take the patient's legs out of the stirrups altogether and have her separate her thighs widely, flex them onto the abdomen, and bear down as in the McRoberts maneuver used in obstetrics. Placing a cylinder, cut from a condom or the finger of a rubber glove, around the blades of the speculum to create a tube will push infolding vaginal walls to the sides and allow visualization of the cervix.[54]

Enlarged or fibroid uteri or severe uterine flexion can increase the difficulty in reaching the gestational sac or completing a procedure. In the case of an enlarged uterus, electric suction may be preferable to manual because there is more length available to reach the sac. A patient with a submucosal fibroid or severe uterine flexion may benefit from the use of a flexible cannula if the fibroid distorts the cavity. In addition, intraoperative ultrasound can provide both guidance and assurance that the abortion is completed.

Ultrasound guidance can be used to facilitate cervical dilation in cases of small cervices. Ultrasound can also be helpful when a pregnancy is located in one uterine horn to ensure complete evacuation. In patients with duplicate cervices, palpation may initially identify the correct cervix. This cervix can then be grasped with an atraumatic tenaculum. If the os is difficult to locate, it can be gently probed with an Osfinder (MedGyn Inc., Lombard, IL) while using ultrasound. It may also be helpful to walk a ring tenaculum around the cervix until the os is visualized.[54]

The Osfinder can also be helpful when cervical stenosis is encountered. These are thin, semirigid tapered dilators with a long graduated tip to slowly dilate the cervical canal. Ultrasound guidance can also be helpful during the dilatation. When dilatation cannot be achieved despite the earlier mentioned efforts, it is best to give vaginal misoprostol 400 mcg, wait 3 to 4 hours, and try again.

Complications

Serious abortion-related complications are rare.[55] In a review of 170,000 procedures before 14 weeks in three clinics in New York City, minor complications were seen in 0.846% of patients and complications requiring hospitalization in 0.071% of patients.[56] The most common complication was mild infection, 0.46%, followed by retained tissue requiring re-evacuation. Other complications include hemorrhage (0.8%), cervical laceration (0.1%), uterine perforation (0.4%), previously undiagnosed ectopic pregnancy, and hematometra. Each of these complications is detailed in the following discussion.

Anticipation of possible complications is the first step in preventing them. Facilities that provide services should have an easily accessible postabortal hemorrhage kit. Among supplies to include are a Foley catheter with a 30 mL balloon, syringe, and sterile water for inflating the balloon; a needle holder, forceps, scissors, and suture for repair of cervical lacerations; uterotonics including Methergine and misoprostol 1000 mcg; equipment for administering IV fluids; and gauze for vaginal packing. If advanced midtrimester D&E is offered, the Bakri Postpartum Balloon (Cook Medical, Bloomington, IN) may be helpful.

Increased bleeding postprocedure may be an indication of an incomplete procedure, uterine atony, uterine perforation, cervical injury, coagulopathy, or a low-lying or placenta accreta. Cervical laceration can be treated with pressure from a ring forceps, Monsel solution, or silver nitrate. If a significant laceration is seen, the extent of the laceration should be identified and the laceration repaired with absorbable sutures.[55]

In cases where the abortion is believed to be complete, uterine massage is a useful next step. Misoprostol 1000 mcg rectally or buccally can be given simultaneously while performing massage. Intramuscular (IM) methylergonovine 0.2 mg can also be given if the patient has no contraindications. If uterine bleeding continues and ultrasound is readily available, a quick survey may document retained tissue or clot (hematometra), which should be evacuated. When brisk bleeding persists after treatment for atony, any retained tissue has been evacuated, and perforation has been ruled out by gentle exploration of the uterine cavity with a blunt instrument, balloon tamponade may well stop the bleeding. A Foley urinary catheter is inserted into the lower uterine segment, and the balloon inflated with water to as much as 70 mL or less if the bleeding ceases. Where possible, the patient is transferred to a hospital and observed overnight. If there is no more significant bleeding, the balloon is partly deflated, and after an hour with no bleeding, completely deflated and removed and the patient sent home (Fig. 13.3).

With refractory bleeding, it is important to obtain a full coagulation profile, hematocrit, and creatinine (if uterine artery embolization is anticipated). Appropriate IV access and aggressive fluid or blood product resuscitation should also be initiated.[55] If the patient can be stabilized and transported to a facility with invasive radiology, it may be possible to terminate the bleeding with uterine artery embolization.[57] If this fails, or is not available, then emergency surgery will be needed. Usually, surgical ligation of bleeding vessels and repair of uterine lacerations will be successful. Postabortal hysterectomy is exceedingly rare and is reported to be as low as 0.01%.[58] These numbers predate the more widespread adoption of uterine artery embolization. The rate of hysterectomy for postabortal hemorrhage is likely even lower today.

Uterine perforation in the first trimester has been reported to occur at rates from 1/10,000 to 1/1000.[58] The severity of injury and site of perforation determines management and treatment. Perforations are often detected when the provider feels a loss of resistance. Severe abdominal pain or the appearance of intra-abdominal contents may also be indicative of a perforation. Perforations in the first trimester usually occur with a sound, dilator, or cannula. With no clinical evidence of intra-abdominal or vascular injury, these patients can be managed expectantly with observation. Large perforations and second-trimester perforations, suspected vascular or intra-abdominal organ injury, an unstable patient, and excessive bleeding should be explored with laparoscopy or laparotomy.

Abdominal pain and fever are a sign of early endometritis. In patients with only a low-grade fever, no signs of sepsis or peritonitis, broad-spectrum oral antibiotics can be used. Signs of sepsis or more severe infection should be managed with hospital admission, IV antibiotics, and fluid resuscitation. Any retained tissue should also be promptly evacuated.[22]

Follow-Up

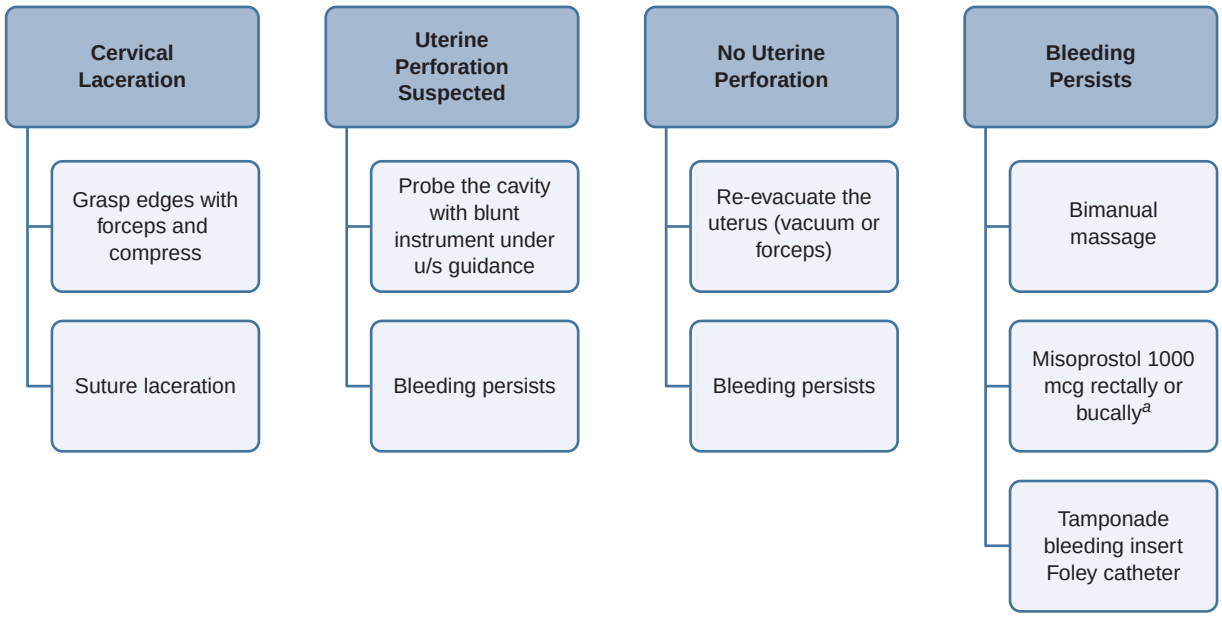
First-trimester abortions do not necessarily require routine follow-up visits. Patients can generally be instructed on how to look for symptoms that may suggest a problem. In addition, this visit can be difficult for the patient by adding additional travel expense, time off from work, and child-care issues. There is also little evidence that these visits do much to detect complications because they often do not occur at the time when complications are most likely to occur. However, for the patient that does return for postprocedural care, this can be an opportunity to review contraception plans, initiate routine gynecologic care, and assess the patient's general well-being following her decision.[59]

MEDICAL ABORTION

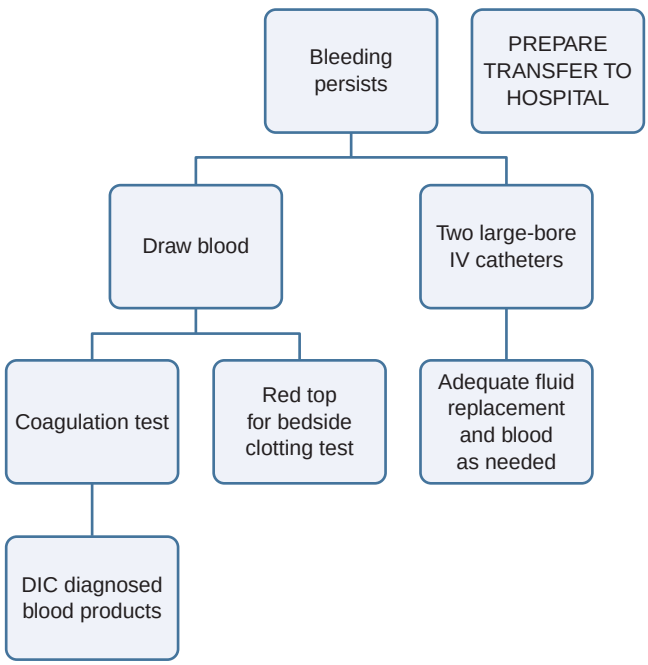
Background

Women have used plants to attempt to abort pregnancies since ancient times, and continue to do so today in traditional societies.[60] However, the first truly safe and effective means for abortion with medication are new. The two-drug combination of mifepristone and misoprostol produces abortion for 95% or more of women treated through 63 days from last menstrual period with no other treatment needed.[61] Side effects other than vaginal bleeding are very rare. Patients can be easily managed in an office setting. In the United States, mifepristone is sold only through physicians who must register with the manufacturer, Danco, Inc. (P.O. Box 4816, New York, NY. www.earlyoptionpill.com).

The following list is just a management suggestion; individual cases may need to be handled differently depending on the cause of bleeding and available resources.



Tamponade bleeding: Insert Foley catheter with 30 mL bag and inflate to 70 mL with sterile water or saline, or less if bleeding stops.



Arrange ambulance transfer of patient to hospital. Prepare for emergency radiologic uterine artery embolization if facilities are available; otherwise, move patient to Operating Suite for emergency surgery.

FIGURE 13.3 Management of excessive bleeding with surgical abortion. [a]We suggest misoprostol because it is readily available out of hospital, inexpensive, stable at room temperature and safe. Other uterotonics that could be used include intravenous (IV) oxytocin, IM 15-methyl prostaglandin $F_{2\alpha}$, or IM methylergonovine if not contraindicated. DIC, disseminated intravascular coagulation.

Physiology and Pharmacokinetics

Mifepristone is a synthetic steroid derived from norethindrone, which blocks the effect of natural progesterone by binding tightly to the progesterone receptor but not activating it. The medication produces a breakdown of capillaries in the decidua of the pregnant uterus, and stimulates prostaglandin synthesis, as well as increases the sensitivity of the uterus to exogenous prostaglandin.[61,62] It has weak antiglucocorticoid effects and has a half-life in humans of 24 to 29 hours. Oral doses of 100 to 800 mg produce similar serum levels. This is attributed to a specific transport protein for mifepristone, which becomes saturated at 100 mg or more. By itself, mifepristone is not a highly effective abortifacient, but when combined with a prostaglandin, very high efficacy is achieved.

Misoprostol (15-deoxy-16-hydroxy-16 methyl prostaglandin E_1) is a synthetic analog of prostaglandin E_1. Its main use is for the prevention of peptic ulcer through its inhibition of gastric acid secretion and mucosa-protective actions. It is widely used in obstetrics for its uterotonic activity and ability to produce cervical softening. At doses that are clinically useful, it has few side effects, is well absorbed orally and vaginally, and unlike other prostaglandins, is stable at room temperature. It is also much less expensive than other prostaglandins, and because of its use to prevent peptic ulcer, is available almost worldwide.[63] It is rapidly absorbed from the gastrointestinal (GI) tract and de-esterified to form an active metabolite, misoprostol acid. After an oral dose, plasma levels rapidly rise and peak at 30 minutes, then rapidly fall. When administered vaginally, plasma concentrations increase more slowly and do not rise as high but remain detectable beyond 6 hours producing an area under the plasma concentration versus time curve (AUC) that is much greater than following oral administration.[64] Sublingual administration produces the highest blood levels, higher than oral administration, and the highest AUC during the first 6 hours.[65] Buccal administration produces blood levels that are lower than after sublingual administration, a pattern similar to that after vaginal administration.[66] Uterine contractility follows the phenomenon seen with plasma levels. Contractility increases more rapidly after oral administration than vaginal, but women given vaginal misoprostol develop uterine contractions that increase continuously over a 4-hour study period. Contractility increases similarly with sublingual administration but diminishes after 3 hours.[66]

Regimens

The initial large clinical trials treated women at 49 days or less since their last menstrual period. Six hundred milligrams of mifepristone was given by mouth, followed by a prostaglandin 48 to 72 hours later. The prostaglandins initially used were either sulprostone IM, or gemeprost vaginal suppositories.[67] Subsequently, misoprostol became the prostaglandin of choice. Misoprostol is much less expensive, is stable at room temperature, and has few side effects at the dose that is effective for abortion. The protocol approved by the U.S. Food and Drug Administration (FDA) is 600 mg of mifepristone orally, followed by 400 mcg of misoprostol by mouth 48 to 72 hours later. During the several years before final FDA approval, investigators demonstrated that a lower dose of mifepristone, 200 mg was just as effective as the 600 mg dose,[68] and that 200 mg of mifepristone plus 800 mcg of misoprostol given by the vaginal route produced complete expulsion of the pregnancy in 96% or more of the subjects in women up to 63 days of amenorrhea.[69,70] This regimen, called the "evidence-based protocol" to distinguish it from the older FDA-approved protocol, has become the most widely used regimen in the United States. The unexpected occurrence of toxic shock with mifepristone and vaginal misoprostol led to concerns that the vaginal route of administration might be a causative factor. Consequently, buccal administration of misoprostol has become for many practitioners in the United States the preferable route.[71]

It was thought initially that mifepristone should be administered 48 to 72 hours before misoprostol in order to allow for disruption of the decidua and increased contractility of the myometrium to develop. However, multiple studies have looked at smaller intervals between doses. The current evidence is that waiting 24 hours after mifepristone before taking misoprostol is sufficient, and in fact, the regimen is almost as effective with a delay of only 15 minutes.[72] In initial trials, the subjects returned to the clinic for administration of the prostaglandin and were then observed until they expelled the pregnancy. Subsequent work established that patients could safely self-administer the misoprostol at home.[73] This is the plan generally followed in the United States.

Alternative Regimens

Although less efficient than mifepristone/misoprostol combinations, misoprostol alone is also effective. Eight hundred micrograms of vaginal misoprostol repeated after 24 hours for two to three doses has been found to produce complete abortion in 88 to 91% of women treated at 56 days or less.[74] The combination of methotrexate followed by misoprostol was thoroughly studied in the United States before mifepristone became available. It is effective in up to 97% of cases, but the abortion process may take as long as 4 weeks to complete.[61,75]

Contraindications

Contraindications to mifepristone/misoprostol for early abortion are listed in Table 13.3. The only one that occurs with any frequency is concomitant corticosteroid therapy. Because mifepristone partially blocks corticosteroid action, there is a theoretical concern that mifepristone could cause transient adrenal insufficiency or

TABLE 13.3 Contraindications to Mifepristone/Misoprostol for Early Abortion

1. Confirmed or suspected ectopic pregnancy
2. Intrauterine device in place. It must be taken out before mifepristone is administered.
3. Concurrent corticosteroid therapy
4. Hemorrhagic disorders or concurrent anticoagulant therapy
5. Not able to return for follow-up visits
6. Not able to access appropriate medical care if an emergency develops
7. History of allergy to mifepristone, misoprostol, or other prostaglandin
8. History of inherited porphyria

From Danco Laboratories. Prescribing Information: Mifeprex (Mifepristone) Tablets. New York: Danco Laboratories. http://www.earlyoptionpill.com/userfiles/file/Mifeprex%20Labeling%204-22-09_Final_doc.pdf. Accessed November 24, 2013.

TABLE 13.4 Summary of Patient Management for Medical Abortion

- Confirm positive pregnancy test.
- Discuss pregnancy options.
- Provide information about medical and surgical abortion.
- Obtain medical history.
- Perform indicated physical exam—at minimum, abdominal and pelvic examination.
- Perform vaginal ultrasound: Confirm intrauterine gestation and estimate gestational age. Provide detailed patient instructions for self-care and follow-up. When to take the misoprostol (usually 24–48 hours after taking the mifepristone):
  a. How to take the misoprostol. (Place two 200 mcg tabs in each cheek pouch, hold for 30 minutes and then swallow them.)
  b. Prescribe oral analgesics (ibuprofen 800 mg, oxycodone 5 mg/acetaminophen 325 mg) and an antiemetic such as prochlorperazine 5 mg orally.
  c. Prescribe antibiotic (doxycycline 100 twice a day for 7 days) taken with food.
  What symptoms to expect, who to call if help is needed, when to call for help
  Heavy bleeding (≥ one pad soaked per hour)
  No bleeding at all by 48 hours of taking misoprostol
  Fever (100.4°F or higher)
  Severe, continuous lower abdominal pain

that the condition being treated with the corticosteroids could flare, but no such events have been reported to date. Although transfusion with medical abortion has been rare, 0.5/1000 patients,[76] women with hemorrhagic disorders or severe anemia would likely be at greater risk for transfusion. Other conditions of concern are treatment with liver enzyme–inducing drugs and preexisting heart disease. A case report of a woman with early pregnancy failure, morbid obesity, and previous myocardial infarction safely managed with 800 mcg of misoprostol is reassuring.[77] Obesity appears to have no impact on outcome of medical abortion. Strafford and colleagues[78] found no difference in need for surgical intervention among women with body mass index (BMI) greater than 30 compared to women with BMI less than 30. All treated with the same dose of mifepristone/misprostol.[78] Twin gestations are treated just as effectively as singletons. The drug regimen need not be modified.

Mifepristone/misoprostol is not an effective treatment for ectopic pregnancy so ectopic should be ruled out prior to initiating a medical abortion. Ectopic pregnancy is a special concern when the patient has a history of bleeding in this pregnancy, has lower abdominal pain, and tenderness on pelvic examination (refer to Chapter 12: Early Pregnancy Failure and Ectopic Pregnancy).

Managing the Patient (See Table 13.4)

As with surgical abortion, the patient should have an opportunity to discuss her feelings about the pregnancy, consider her options of continuing the pregnancy, adoption, or terminating by medical or surgical means. Ideally, patients considering abortion should be able to choose between medical and surgical methods and should be given information about both.[61]

A pregnancy test, medical history, pregnancy history, and indicated physical exam including a pelvic exam are needed. A hemoglobin or hematocrit, blood group, and Rh status are usually determined. A vaginal ultrasound is typically obtained to confirm intrauterine pregnancy and for dating. In many countries, clinicians manage medical abortion successfully without routine ultrasound, relying on the patient's history, a positive pregnancy test, a pelvic exam to confirm intrauterine gestation and determine the gestational age, and then a pelvic exam to confirm successful abortion.[79] The gestational age limit of 63 days for patients managed in the office or at home has been proven safe; however, the same drugs are effective at later gestations and have been studied to 24 menstrual weeks with hospitalized patients.[80] As gestational age advances, more doses of misoprostol are needed, the probability of complete abortion without surgical assistance falls, and the amount of bleeding increases.

Mifepristone is administered in the office. The patient is usually instructed to take the misoprostol 24 to 72 hours later, when she is in a safe and comfortable surrounding, because expulsion of the pregnancy often occurs within 4 to 6 hours of taking the misoprostol. With buccal administration, the patient is instructed to place two 200 mcg misoprostol tablets in each cheek pouch and keep them there for 30 minutes before swallowing the tablets. Patients who are Rh negative should receive Rh-immune globulin when they receive their mifepristone dose.

Women undergoing medical abortion may experience severe pain. About 75% of patients will use a narcotic analgesic on the day of misoprostol administration.[81] Many providers give patients prescriptions for an NSAID and for a narcotic/NSAID combination analgesic (e.g., oxycodone 5 mg/acetaminophen 325 mg). Taking a dose of the NSAID by mouth just before inserting the misoprostol may reduce pain and does not appear to reduce the efficacy of the misoprostol. Patients can be instructed to take the narcotic combination as needed. Some providers routinely prescribe an oral antiemetic to use in cases of persistent nausea or vomiting (e.g., prochlorperazine maleate 5 mg).

Prophylactic antibiotics are becoming increasingly common after a few case reports of death from a rare but serious infection following medical abortion. The large Planned Parenthood cohort study has shown that changing from vaginal misoprostol to buccal administration, plus routine prescription of doxycycline 100 mg twice a day for 7 days reduces the incidence of serious infection from 0.93 per 1000 to 0.07 per 1000.[71] Patients should be advised to eat a small amount before taking doxycycline to avoid gastric irritation that is common if taken on an empty stomach. Patients are also cautioned to avoid sun exposure while taking doxycycline.

It is important to carefully counsel patients on what to expect with a medical abortion and for what side effects they should seek medical help. Patients may experience some vaginal bleeding within a few hours of taking mifepristone, and a small proportion will go on to abort before receiving misoprostol. In most cases, significant cramping pain begins soon after the misoprostol is taken. This is followed by slowly increasing severity of cramps and then vaginal bleeding. Bleeding is generally no more than that of a heavy menstrual period. The bleeding and cramping become much less after the pregnancy is expelled, although some bleeding is common for 2 weeks after treatment. Patients are cautioned that if they have bleeding heavy enough to soak through a menstrual pad several hours in a row, they should seek medical attention. If there is no bleeding within 24 to 48 hours after taking misoprostol, patients should return to the office for evaluation because this may indicate a failed abortion. Misoprostol at the 800 mcg dose may produce a low-grade fever. Patients should seek medical help if they feel feverish and their temperature exceeds 100.4°F. Flulike symptoms and severe unremitting pain in the lower abdomen that persists for several hours are not normal and can be a sign of sepsis. Patients should be told to seek medical help for these symptoms, even if there is no fever.[82,83]

Patients should return for follow-up in about 1 to 2 weeks. The history of bleeding, cramping, and passage of tissue should be recorded. Studies have reported a 99.1% accuracy in determining medical abortion completion when both the clinician and patient felt that the sac had passed.[84] In the United States, patients usually have a vaginal ultrasound at this time. For patients in which returning to the office would be difficult or in low-resource settings where ultrasound is not readily available, management can be done with the use of serial beta-hCG titers. Blood is drawn for a beta-hCG titer on the day of mifepristone treatment and then repeated on days 6 to 18 after mifepristone is administered. A fall of 80% is a highly reliable indicator of a complete abortion.[85] Clark and colleagues[86] have demonstrated that a combination of women's observations, a low-sensitivity pregnancy test, and a clinical examination correctly identified women who required intervention at or after the follow-up visit, without an ultrasound, and detected all of the ongoing pregnancies.

An ultrasound will most likely show the presence of some heterogenous material in the uterine cavity. Measurement of the endometrial stripe is of little clinical use. As long as there is no gestational sac present and the patient has minimal bleeding, she can be managed expectantly. If bleeding is heavy, treatment can be offered with either a repeat dose of buccal misoprostol 800 mcg or office uterine aspiration under local anesthesia, with or without IV sedation, depending on the severity of the symptoms and patient preference. If a gestational sac is still present but there is no fetal heartbeat, the patient can be managed as discussed earlier with either misoprostol or surgical aspiration. If a fetal heartbeat is still present, the medical abortion is considered failed. The patient should be offered surgical uterine aspiration. If abortion has failed and the pregnancy continues, the patient may need a late abortion or may continue on to delivery. Patients with a failed medical abortion and a continued pregnancy should be counseled that misoprostol can be teratogenic.[76]

Complications of Early Medical Abortion

The most common complication seen with early medication abortion is excessive bleeding.[86] In a series of 95,163 mifepristone/misoprostol abortions from the Planned Parenthood Federation of America clinics, 206 women (2 per 1000) required hospital care, either just treatment in an emergency room or admission.[71] A little over half (1.3 per 1000) were seen because of heavy bleeding. Of these, about half needed a transfusion. Most were treated with surgical uterine evacuation. Infection requiring hospital care occurred in 2 per 10,000, and sepsis occurred in 2 per 100,000 cases. One death occurred from septic shock (1.1 per 100,000).[71]

Where patients with heavy bleeding can be seen in the office, they can be treated immediately by a simple uterine aspiration and spared a hospital visit. Similarly, patients with signs of early endomyometritis may be treated successfully with an office uterine aspiration and an oral antibiotic regimen.[86]

Toxic Shock

Toxic shock is a rare complication of medical or surgical abortion, childbirth, and surgery.[87] In 2005, the CDC reported four deaths in California and one in Canada from sepsis with *Clostridium sordellii*, a Gram-positive toxin-forming anaerobic bacterium.[88] All had been treated with mifepristone 200 mg and vaginal misoprostol. The abortion patients with *C. sordellii* sepsis typically presented with malaise, severe lower abdominal pain, tachycardia, and hypotension. Blood count revealed an extreme leukocytosis and a marked elevation of hematocrit from hemoconcentration.[82] Whether the vaginal administration of misoprostol led to these infections has not been determined; however, there is evidence from animal studies that it might.[89] As discussed previously, vaginal misoprostol has largely been replaced in

the United States by buccal administration. Despite this change, one additional case of *C. sordellii* sepsis has occurred in a non–Planned Parenthood patient treated with buccal misoprostol who did not receive prophylactic antibiotics.[71] These cases are exceedingly rare. Only one case has been reported outside of California, the Canadian case, and none from Europe or the rest of the world.[82] A California study found fatal *C. sordellii* sepsis not only in the medical abortion cases cited earlier but also in pregnant women not treated with mifepristone, in women who had not been recently pregnant, and after gynecologic surgical procedures.[90] This group estimated the population-based risk of *C. sordellii* sepsis as 0.036 per 100,000 persons. Hopefully, the combination of buccal misoprostol and prophylactic doxycycline will prevent future cases of *C. sordellii* toxic shock associated with medical abortion. However, patients must be informed to seek medical help if they experience the unusual symptoms described earlier.

SECOND-TRIMESTER TECHNIQUE

Although second-trimester procedures are far less common than procedures performed in the first trimester, they remain a significant portion of all abortions provided. Many of these procedures are in women whose fetuses have been diagnosed with congenital anomalies, who have serious medical illnesses themselves, or who are disproportionately very young.[22] Most second-trimester procedures are now done by D&E. A series of studies proved their safety over labor inductions.[89] A small proportion of patients still request labor induction. For some patients, including those with morbid obesity where visualization of the cervix and ultrasonographic visualization of the pregnancy is challenging, this can be a safer method. In addition, in centers where experienced midtrimester providers are not available, labor induction remains a viable and safe option.

With careful patient selection, second-trimester D&E can be safer and less expensive in a dedicated outpatient facility than in a hospital setting.[91] For outpatient clinic settings, it is necessary to have skilled providers, the means to provide adequate anesthesia with appropriate monitoring, a dedicated area for recovery, support staff able to provide pre- and postprocedural care, and a protocol for transferring patients to a nearby hospital if needed.[51]

Routine use of cervical preparation with either medical or mechanical agents decreases the risk of cervical and uterine trauma.[47] Typical forceps used in D&E procedures range from 14 to 19 mm, so dilatation should be at least sufficient to pass these instruments. Later gestations may require even more dilatation. Only one randomized trial has compared misoprostol to overnight laminaria in early second-trimester D&Es. Greater dilatation and greater provider satisfaction was found with overnight laminaria as compared to misoprostol in patients between 13 and 16 weeks' gestation.[92] In patients greater than 20 weeks' gestation, osmotic dilators may be preferable to misoprostol.[48]

Currently, laminaria and Dilapan-S are available as osmotic dilators. Laminaria are tents made of dried, compressed seaweed stem. They absorb fluid and gradually expand to dilate the cervix. They also induce endogenous prostaglandins to aid in cervical softening. Laminaria come in sizes from 2 to 10 mm. They slowly swell to three to four times their original diameter. The majority of dilatation occurs within 6 hours; however, the maximum effect is seen in 12 to 24 hours. Dilapan-S is a hygroscopic rod dilator composed of hydrophilic polymers. They are available in 3 to 5 mm sizes. They also swell to three to four times their original diameter. The majority of dilatation is seen in 4 to 6 hours, but they can be left in for up to 24 hours with some clinical effect.[93,94] The older Dilapan that were available prior to 2002 had the propensity to break during removal, leaving the possibility of retained fragments.[95] Although Dilapan-S has a stronger core, there are reports of fragmentation with this formulation as well. Dilapan-S may achieve more rapid dilatation and may allow for fewer overall dilators being placed.[94] The choice of dilator is often left to provider preference. Some providers use a combination of both types of dilators.

Dilator placement is an office procedure. Risks associated with dilator placement are low but should be included in counseling. These include a risk of spontaneous labor, less than 1 in 2000 to 3000 from 14 to 18 weeks and 1 in 500 at later gestations, difficult removal, hypersensitivity to laminaria, vasovagal reactions, membrane rupture, and cervical lacerations.[94]

For dilator placement, a speculum is placed in the vagina, the cervix and vagina are cleansed with povidone-iodine or chlorhexidine solution, a single tooth tenaculum or atraumatic tenaculum is used to grasp the anterior lip of the cervix, and using ring forceps or a long Kelly uterine forceps, dilators are serially placed. Pain relief during placement can be accomplished with administration of an NSAID in addition to a paracervical block with 1% lidocaine. The number of dilators placed varies depending on gestational age, the parity of the patient, and the type of dilators used. Many different protocols exist for how many dilators should be placed. In general, providers attempt to place the maximum number of dilators that can be inserted without excessive force.[48] Some use the gestational age minus 10 as a rough guide as to the number of dilators to use (e.g., at 18 weeks, place eight dilators). In patients over 20 weeks' gestation, some providers routinely do serial dilator placement. A first set is inserted on day 1 and then removed on day 2, and a second set of a greater number of dilators is inserted the next day as the cervix becomes softer and begins to dilate. In a randomized trial of laminaria placement from 17 to 19 weeks, a 2-day protocol led to a greater degree of dilatation, but the added discomfort and patient

inconvenience from this regimen was questioned by the authors.[96] To remove the dilators prior to the procedure, the provider should attempt to gently pull on the dilators with two fingers. If removal is not easily achieved, a speculum can be inserted and a ring forceps used to grasp one dilator at a time. It is important to have careful documentation of the number of dilators inserted and then subsequently removed. After insertion, patients should be given careful instructions to return to the facility or to a hospital if they develop signs of labor or infection.

Procedures up to 16 weeks' gestation can be performed using vacuum aspiration with an appropriately sized cannula, with small forceps or with a combination of the two. After 16 weeks' gestation, most D&Es are done using forceps extraction. Ultrasound guidance is increasingly used for second-trimester procedures but is not a requirement with skilled providers. Ultrasound should, however, be readily available in facilities offering these procedures. Before performing these procedures, the provider should seek advanced training when this can be found. Unfortunately, second-trimester procedures are taught in only a few general obstetrics and gynecology residency programs. Clinicians without access to specialized training may move into providing second-trimester procedures by becoming adept at first-trimester procedures and then slowly increasing their gestational age limits, preferably using ultrasound guidance.

CONTRACEPTION

Discussion regarding contraception should be initiated at a patient's preoperative visit before surgical abortion. All appropriate options should be discussed. Patients choosing oral contraceptives, the patch, or the vaginal ring can begin their method the day of the procedure. The first ring can be placed in the vagina at the end of the procedure if the patient wishes. The first depot medroxyprogesterone acetate injection can be given immediately after the procedure. Similarly, either the levonorgestrel intrauterine device (IUD) or the copper-containing device can be inserted at the completion of the procedure, before the speculum and tenaculum are removed. The subdermal implant (Nexplanon) can also be inserted immediately postabortion. Providing the patient with immediate postabortal IUDs or an implant offers the considerable advantages of long-term contraception. In the first trimester, risks of perforation from an IUD, expulsion, infection, and failure are low and are similar to interval insertion. There may be a slightly higher IUD expulsion rate in the second trimester but still the benefits of immediate effective contraception generally outweigh this risk.[97,98] Patients interested in sterilization should be counseled appropriately and given a temporary contraceptive method to protect them until the sterilization can be arranged.

Patients choosing medical abortion should be given contraceptive counseling and a method prescribed at the time of the initial treatment. Contraception should not be left for the postabortal visit because many patients do not return, and ovulation may occur as soon as 14 days after medical or surgical abortion. The oral contraceptive, the contraceptive patch, and the vaginal ring can be started any time after expulsion of the pregnancy. Patients choosing injectable depot medroxyprogesterone acetate, the subdermal implant, or the IUD can be advised to use condoms until confirmation that the pregnancy has passed.

CLINICAL NOTES

- Safe abortion services can be readily provided in an office setting.
- Prophylactic antibiotics are recommended with both surgical and medical abortion.
- There are few contraindications to clinic or office abortions; however, patients with serious pre-existing medical conditions are best managed in a hospital setting when this is possible.
- Pain relief for surgical abortions includes a preoperative NSAID, paracervical block, and optionally, IV conscious sedation with monitoring that includes continuous pulse oximetry.
- Manual vacuum supplied with a modified syringe is equivalent to vacuum generated by an electric pump for first-trimester surgical procedures and is portable, silent, and much less expensive.
- The MVA technology is also useful for treating menorrhagia and spontaneous abortion in the office.
- Preoperative preparation of the cervix with misoprostol or laminaria tents is advised at 12 to 14 weeks' gestation and beyond.
- After completing the surgical procedure, the operator should perform an inspection of the aspirated tissue in a glass dish over a source of backlighting.
- Obesity adds to the difficulty of surgical abortion and may require positioning the patient with her thighs flexed on the trunk and the use of long instruments.
- Ultrasound guidance during a procedure can be helpful in patients with small cervices, extreme uterine flexion, uterine duplication, or large fibroids.

(continues)

- Management of postabortal hemorrhage is facilitated by an accessible kit of instruments and medications.
- Steps in managing uterine hemorrhage include completely evacuating the uterus, uterine massage, administration of uterotonics, balloon tamponade of the uterus, and transfer to a hospital for uterine artery embolization or surgery.
- Medical abortion with mifepristone and misoprostol is highly effective up to 63 days' gestation.
- The present evidence-based protocol for medical abortion in the United States includes 200 mg of oral mifepristone followed at 24 to 48 hours by misoprostol 800 mcg self-administered by the buccal route.
- Pain relief for medical abortion includes NSAIDs and oral narcotic agents.
- Patients require clinical evaluation 1 to 2 weeks after a medical abortion to verify that complete expulsion has occurred.
- Complete expulsion can be verified by either a transvaginal ultrasound or serial beta-hCG titers.
- The most common complication of medical abortion is heavy bleeding. This can usually be treated with office vacuum aspiration.
- *C. sordellii* toxic shock is a very rare complication of medical abortion. Present protocols using misoprostol by the buccal route and prophylactic antibiotics may prevent this.
- Second-trimester abortion by D&E after cervical preparation with laminaria or misoprostol can be safely provided in an office setting with proper equipment and staffing.
- Because ovulation can occur as soon as 14 days after first-trimester abortion, contraception should be supplied to all patients at the time of treatment.
- IUDs can safely be placed at the time of a surgical abortion or after verification of a completed medical abortion.

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CHAPTER 14

Benign Disorders of the Vulva and Vagina

Colleen Kennedy Stockdale and Lori A. Boardman

INTRODUCTION

Vulvovaginal symptoms are common, often chronic, and can significantly interfere with sexual function and sense of well-being. Despite this, vulvovaginal symptoms are often underreported by women. Thus, when identified, vulvovaginal symptoms should be addressed by providers (including referral) to optimize care. In clinics specializing in the evaluation of women with vulvar complaints, the most common symptoms reported were vulvar pain, dyspareunia, and pruritus, with dermatologic conditions and vulvodynia (both generalized and localized forms) leading the diagnoses rendered.[1]

Understanding of the differences in epithelial and glandular structure, hormonal responsiveness, neural distribution, and immune responses is necessary when assessing vulvar complaints. For instance, the nonkeratinized vestibule is more permeable than keratinized skin, whereas the labia majora displays elevated hydration, occlusion, and frictional properties, all of which may increase irritant (chemical and mechanical) susceptibility.

Important vulvar landmarks include the labia majora, prominent hair-bearing folds of skin that represent the lateral boundaries of the vulva and meet to form the anterior boundary of the vulva at the mons pubis. Fusion of the labia majora at the fourchette determines the posterior boundary of the vulva. The non–hair-bearing labia minora lie medial to the labia majora and fuse anteriorly to form the prepuce and frenulum of the clitoris and thus mark the superior boundary of the vestibule (opening to the vagina). The vestibule is bound medially by the hymen and laterally by Hart's line, a variably distinct line of demarcation evident at the base of the medial aspect of each labium minus. Hart's line separates the nonkeratinized squamous epithelium of the vestibule from the keratinized epithelium of the more lateral labia minora and serves as an important landmark for several of the disorders discussed (Fig. 14.1).

When taking a history, it is important to ask about the onset, duration, location, and nature of vulvar symptoms (including the relationship of symptoms to the patient's menstrual cycle) as well as any possible precipitating factors (including medications employed to reduce symptoms). In the evaluation of infectious causes of vulvovaginal complaints, microscopy, in conjunction with vaginal pH determination, helps guide the use of subsequent diagnostic tools, including vaginal fungal cultures, a variety of U.S. Food and Drug Administration (FDA)-approved point-of-care tests, culture or polymerase chain reaction (PCR) for confirmation of herpes simplex virus, and specific serologic tests.[2,3] Examination of other skin sites such as the mouth, eyes, and scalp should also be done as non–genital-based disease may present with manifestations in the vulvar or vaginal areas. For autoimmune disorders and suspected cases of neoplasia, biopsy is invaluable.

Pruritus

In evaluating vulvar pruritus, it can be helpful to group women into those with acute versus chronic symptoms. Acute anogenital pruritus is most often infectious (as covered in Chapter 4: Vulvovaginitis and Chapter 6: Sexually Transmitted Infections and Pelvic Inflammatory Disease) with allergic and irritant contact dermatitis playing a role in some cases. Chronic pruritus, in general, has a history of gradual onset; examples of which include lichen simplex chronicus, lichen sclerosus, psoriasis, and various manifestations of human papillomavirus–related disease.

RECURRENT VULVOVAGINAL CANDIDIASIS

Candidiasis is the most common chief complaint by women presenting with vulvovaginal symptoms. A thorough history and evaluation are imperative for diagnosis. Most candidal infections are sporadic and, in more than 90% of cases, are caused by *Candida albicans*. Women with recurrent disease present a challenge both in terms of evaluation and treatment. Although testing for diabetes or immunosuppression is often suggested, such testing is rarely helpful. On the other hand, host factors, such as uncontrolled diabetes, immunosuppression, repeated exposure to antibacterials, and exogenous estrogen exposure may all be responsible for recurring episodes. Although non-albicans species should be suspected and culture is clearly warranted in this population, it should be remembered that repeated vulvovaginitis most commonly

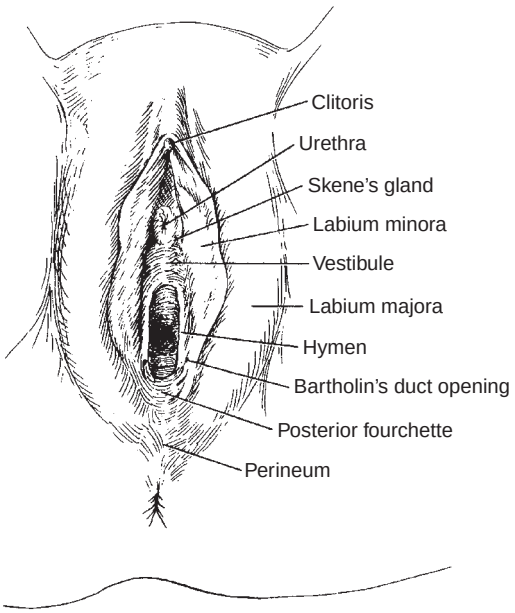

FIGURE 14.1 Normal anatomy. (From Beckmann CRB, Ling FW, Barzansky BM, et al. *Obstetrics and Gynecology*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.)

occurs with persistent *C. albicans*, with non-albicans *Candida* species seen in approximately 10 to 20% of women with recurrent disease.

A reliable diagnosis cannot be made based on symptoms or signs in the absence of corroborative laboratory data. In addition to direct microscopy, patients should have vaginal cultures obtained on at least two occasions, preferably while symptomatic. If two consecutively obtained cultures are negative for *Candida* species, the diagnosis of recurrent disease can be confidently excluded and other infectious (e.g., recurrent bacterial vaginosis, resistant trichomoniasis) and noninfectious (contact dermatitis, atrophic vaginitis, desquamative inflammatory vaginitis) etiologies should be considered.[4]

Recurrent infection with *C. albicans* can be treated with the same regimen used for severe disease (a 7- to 14-day course of a topical azole or two sequential doses of fluconazole), followed by 6 months of maintenance therapy with either oral medication (weekly fluconazole) or clotrimazole (weekly suppository).[5] In a recent randomized controlled trial of suppressive therapy with fluconazole, women with recurrent disease on maintenance medication for 6 months, compared with those on placebo, were significantly more likely to remain disease-free at both 6 months (91% versus 36%) and at follow-up off medication 6 months later (43% versus 22%).[5]

Non-albicans infections (e.g., *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*) typically do not respond to treatment with fluconazole, often secondary to an intrinsic resistance to this medication. Recommended therapy, then, is a 7- to 14-day course of a nonfluconazole azole. If treatment fails, a 2-week course of nightly boric acid vaginal suppositories (600 mg in a 0 gel capsule) or nightly 4% flucytosine vaginal cream (requires a compounding pharmacy) can be used.[6]

VULVOVAGINAL EPITHELIAL DISORDERS

Human Papillomavirus–Related Disease

Genital human papillomavirus (HPV), the most common sexually transmitted viral infection, is associated with a number of vulvar and vaginal epithelial disorders, including genital warts, vulvar and vaginal intraepithelial neoplasia, and some carcinomas. Of the more than 120 HPV subtypes identified, more than 40 are specific to the anogenital tract, and of those, at least 15 are believed to be oncogenic. Commercially available probes for HPV DNA typing allow for identification of half of these anogenital subtypes, including 5 low-risk and 14 oncogenic subtypes. Although low-risk HPV types 6 and 11 are implicated in the development of genital warts and oncogenic HPV 16 commonly is found in classic (bowenoid) vulvar intraepithelial neoplasia (VIN), routine use of HPV testing for diagnosing vulvar HPV-related disease is not recommended at this time.

Estimates of the prevalence of HPV infection cannot be derived from visible manifestations of disease alone because the majority of infections are subclinical. Approximately 1% of women will develop condyloma, and few will develop dysplasia. Estimates suggest that HPV infection is associated with approximately 40% of vulvar cancers, compared to nearly 100% of cervical squamous cell cancers.[7] In contrast to the typical keratinizing vulvar squamous carcinomas seen in older women (in which oncogenic HPV infection ranges from 2 to 23%), HPV-related basaloid and warty carcinomas (75 to 100% of which are associated with oncogenic HPV) tend to arise in younger women.[7]

When clinical manifestations of vulvar HPV infection do occur, they often present as bumps or growths on the vulvovaginal or perianal epithelium. Commonly asymptomatic, genital warts are as likely to cause itching, burning, pain, or bleeding. On examination, warts can range in morphologic appearance from flat-topped papules to flesh-colored, dome-shaped papules, keratotic warts, or true condylomata acuminata (Fig. 14.2). External genital warts tend to occur on the moist surfaces of the vulva, introitus, and perianal area. Distinguishing warts from vulvar neoplasia based on appearance alone is not always possible. If the diagnosis is uncertain, or the patient is immunocompromised, biopsy should be undertaken.[2]

Women with genital warts should undergo routine cervical cancer screening. By the same token, the use of HPV testing, a change in the frequency of cervical cytologic screening or cervical colposcopy are not indicated in the presence of genital warts unless exophytic cervical warts or vulvar neoplasia is confirmed by biopsy; in which case, referral for colposcopic evaluation is indicated.[2]

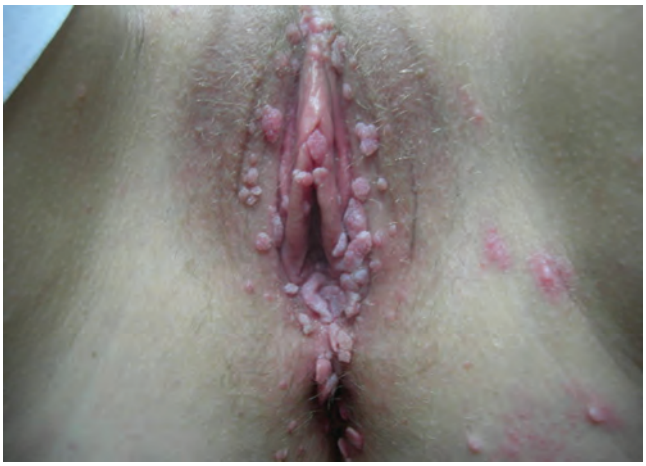

FIGURE 14.2 Condyloma. (Multiple flat-topped papules and verrucous lesions.) (From C. K. Stockdale personal library.)

Spontaneous regression of genital warts occurs in up to 30% of affected patients. Despite this, many women opt for intervention to shorten the duration of lesions. It is important to note that regression does not necessarily lead to viral clearance because viral genomes can be detected in normal epithelium for months to years following clearing of visible disease. In immunocompetent women, however, the cell-mediated immunity that resulted in lesion regression most likely controls latent HPV infection. Disease recurrence is, therefore, less likely. Women at increased risk of developing HPV-related manifestations thus include those receiving long-term corticosteroid therapy or chronic immunosuppressive treatment as well as immunosuppressed women with HIV infection. Antiviral chemotherapies are particularly critical for these populations if disease recurrences are to be minimized.[8] However, most currently available treatment options are directed toward removal of visible disease rather than eradication of HPV infection.

Treatments endorsed by the Centers for Disease Control and Prevention include podofilox 0.5% solution or gel (patient-applied) as well as the provider-administered therapies: cryotherapy, podophyllin resin 10 to 25%, trichloroacetic or bichloroacetic acid 80 to 90%, surgical removal, and laser therapy.[2] Such therapies have been the mainstay of treatment, along with imiquimod, a targeted antiviral therapy. Although most treatments are equivalent in terms of clearance rates, recurrence rates can be high, particularly for laser therapy where the recurrence rate exceeds 60%. However, imiquimod has been demonstrated to have significantly lower recurrence rates (9 to 19%).[7]

Intralesional interferon, a medication with antiproliferative, antiviral, and immunomodulatory properties, has, unlike imiquimod, demonstrated limited efficacy and is not recommended for first-line therapy in treating either warts or VIN.[8] Its use, however, can be considered an alternative regimen for the treatment of external genital warts.[2] The most recent FDA-approved patient-applied treatment for external condyloma is Veregen 15% topical ointment (Doak Dermatologics, Fairfield, NJ), a class of sinecatechins. This class of drugs is a mixture of catechins and other green tea components and has a response rate up to 55% complete clearance and 78% reduction of external anogenital warts with short-term follow-up.[7]

Because of decreased immune function, condyloma burden may exacerbate during pregnancy. Treatment is limited to expectant management or locally destructive options. Podofilox, podophyllin, and imiquimod are recognized teratogens and are therefore not recommended for use in pregnancy. Additionally, the risk of HPV appears inconsistent following vaginal delivery and does not justify routine cesarean birth in women with genital warts.[2]

Vulvar Intraepithelial Neoplasia

The most common symptom of VIN is pruritus. The incidence of VIN has increased over 400% since the 1970s especially among younger women.[7] In 2004, the Vulvar Oncology Subcommittee of the International Society for the Study of Vulvar Diseases (ISSVD) developed the current classification system for VIN[9] (Table 14.1). In this classification system, two distinct clinicopathologic subtypes of VIN exist: (a) VIN, usual type, which encompasses the former subcategories of VIN, warty type; VIN, basaloid type; and VIN, mixed (warty, basaloid) type; and (b) VIN, differentiated type, which encompasses the former category simplex type. Previously, VIN was categorized as VIN I, II, and III according to the degree of abnormality. In the new classification system, the term VIN is limited to histologically high-grade

TABLE 14.1 Classification of Vulvar "Dystrophy" and Squamous Vulvar Intraepithelial Neoplasia

"Dystrophic" conditions
Lichen sclerosus
Squamous cell hyperplasia (hyperplastic "dystrophy")
Mixed lichen sclerosus and squamous hyperplasia
Squamous vulvar intraepithelial neoplasia grade I (VIN I, low-grade VIN)
Squamous vulvar intraepithelial neoplasia using ISSVD 2004 modified terminology (includes only VIN II/III or high-grade VIN)
VIN, usual type
VIN, warty type
VIN, basaloid type
VIN, mixed (warty/basaloid) type
VIN, differentiated type (previously carcinoma in situ differentiated or simplex type)

VIN, vulvar intraepithelial neoplasia; ISSVD, International Society for the Study of Vulvar Disease.

Data from Sideri M, Jones RW, Wilkinson EJ, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med.* 2005;50(11):807–810; Stoler MH, Mills SE. The vulva and vagina. In: Mills SE, ed. *Sternberg's Diagnostic Surgical Pathology.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2010:2106.

squamous lesions (formerly termed VIN II and VIN III) for which treatment is indicated to prevent progression to cancer.

Usual type VIN, which includes warty-bowenoid or mixed type as well as pure warty and pure basaloid types, includes both VIN II and III, is HPV-related, commonly presents in women in their 30s and 40s, tends to be multifocal, and is strongly associated with cigarette smoking.[10] Risk for usual type VIN is also increased in women who are immunosuppressed or immunodeficient.[11] The interlabial grooves, posterior fourchette, and perineum are most frequently affected by multifocal lesions and more extensive disease is often confluent, involving the labia minora and majora as well as the perianal skin. Multifocal sites or confluence of usual type VIN is seen in up to 67% of women with usual VIN (Figs. 14.3 through 14.5).

Usual type VIN is more common than differentiated VIN and accounts for at least 90% of cases of VIN. It is strongly HPV associated, with HPV-16 implicated in 70% of cases.[12] Patients often have a history of condyloma, sexually transmitted infections, and HIV-positive status. Less than 10% of women with warty-bowenoid VIN develop invasive squamous cell carcinoma (SCC).[13] Younger women with multifocal, small, papular, pigmented lesions (a clinical entity referred to as bowenoid papulosis; Fig. 14.6) are the most likely to experience spontaneous resolution of the lesions, particularly if they are pregnant or postpartum at the time of diagnosis.[14] In contrast, women older than 40 years of age and those who are immunosuppressed are at the greatest risk of progression.

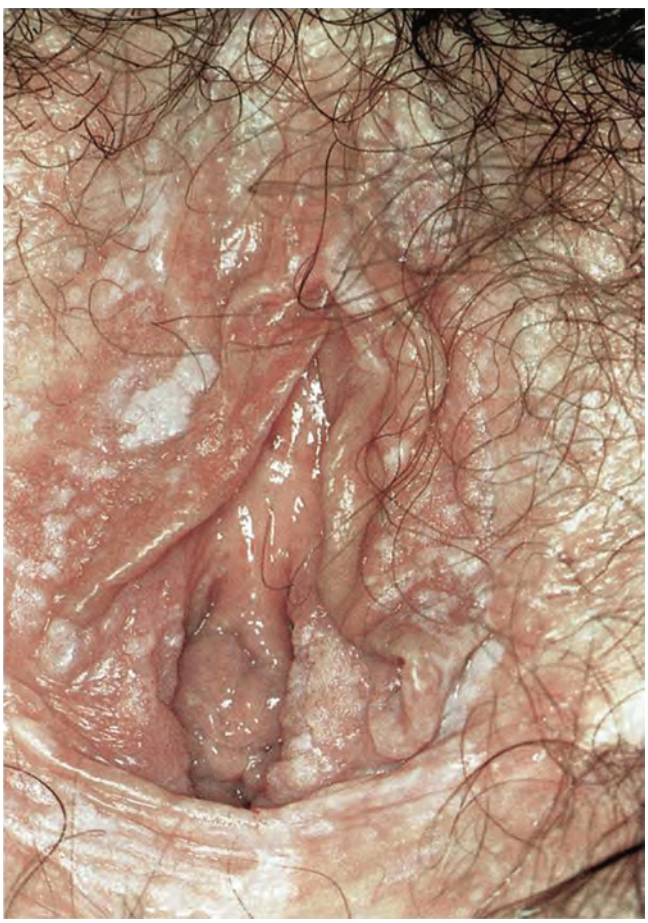

FIGURE 14.3 Diffuse plaques of white epithelium in a 25-year-old woman with history of two prior laser treatments. Biopsies demonstrated VIN II (polymerase chain reaction was positive for HPV 16/18). (From Wilkinson EJ, Stone IK, eds. *Atlas of Vulvar Disease*. Philadelphia: Lippincott Williams & Wilkins; 2012:92.)

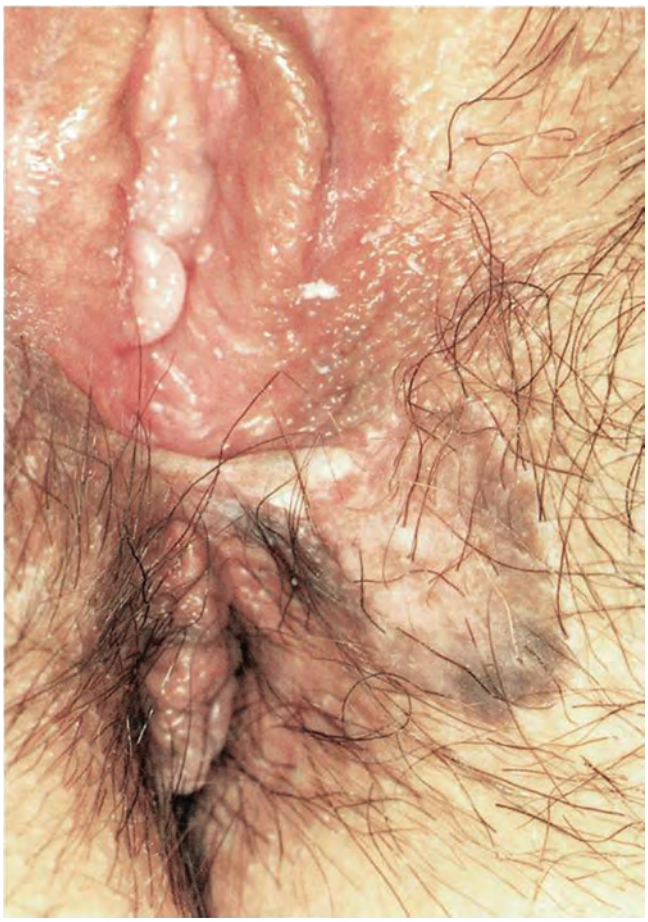

FIGURE 14.4 Hyperpigmented, localized lesion in an asymptomatic patient. Biopsy demonstrated VIN II/III, and the lesion was excised under general anesthesia and confirmation of diagnosis. Skin was undermined and closed with a permanent suture, which was removed 10 days later. (From Wilkinson EJ, Stone IK, eds. *Atlas of Vulvar Disease*. Philadelphia: Lippincott Williams & Wilkins; 2012:92.)

Differentiated VIN, which includes simplex VIN, is typically HPV negative, is seen most frequently in older women with other epithelial disorders such as lichen sclerosus or lichen simplex chronicus and is usually unifocal and unicentric. Although simplex VIN accounts for only 2 to 10% of biopsy specimens with VIN, it is more likely to progress to SCC than classic VIN. In one review looking at the natural history of differentiated VIN, 9% of untreated patients progressed to invasive vulvar carcinoma compared to 3.3% of treated patients.[15,16] Differentiated VIN often occurs adjacent to invasive

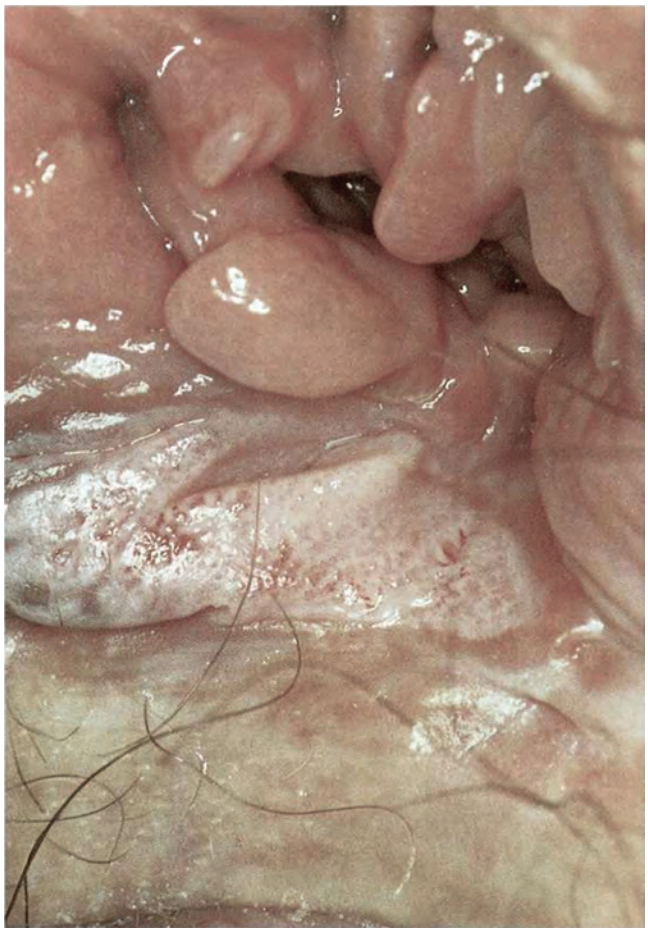

FIGURE 14.5 Thickened white epithelium at introitus. Note prominent fissure. Excisional biopsy demonstrated VIN III. (From Wilkinson EJ, Stone IK, eds. *Atlas of Vulvar Disease*. Philadelphia: Lippincott Williams & Wilkins; 2012:93.)

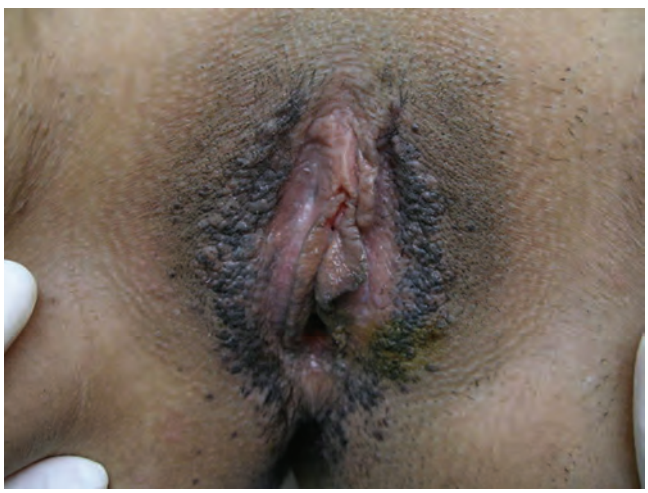

FIGURE 14.6 Vulvar intraepithelial neoplasia III. (Warty-bowenoid VIN; diffuse brown hyperpigmented raised papules.) (From C. K. Stockdale personal library.)

SCC of the vulva and is thus regarded as the most common precursor to vulvar SCC. It may be often underdiagnosed.[17] By definition, simplex VIN is a high-grade lesion and warrants further evaluation and treatment. In general, differentiated VIN lesions are smaller and less bulky than warty-baseloid VIN lesions, and often appear as gray-white lesions with roughened surfaces or as raised white plaques or nodules. It is often found during surveillance examinations for women with a history of lichen sclerosus or vulvar SCC. All suspicious lesions of the vulva should be biopsied.

VIN is highly variable in its gross appearance; because the lesions may be subclinical, they may only be apparent with colposcopy. Because the prevalence of multifocal lesions is high, comprehensive colposcopic examination of the entire lower genital tract and perianal area is indicated in any woman with VIN. The most common findings noted on the vulva during examination with the colposcope are areas of acetowhitening that may or may not have areas of punctation. When using colposcopy to evaluate for VIN, it is important to remember that the vulvar area must be soaked with 2 to 5% acetic acid for about 5 minutes. Acetowhite changes do not determine the diagnosis; rather, they are nonspecific and only serve to indicate where biopsies should be taken. Raised acetowhite areas, particularly in conjunction with small papillations or satellite lesions, suggest HPV changes. Lesions that are hyperpigmented, fixed, indurated, or ulcerated, as well as condylomas that do not respond to therapy warrant biopsy evaluation. Vulvar punch biopsies are usually done with the Keys dermatologic biopsy instrument because it allows for full-thickness evaluation of the vulva skin as well as accurate orientation of the specimen. Multiple biopsies may be required when there are multifocal lesions. Bleeding from the biopsy site is usually controlled with ferric subsulfate (Monsel solution) or silver nitrate sticks; rarely are sutures necessary. If a punch biopsy does not yield a satisfactory specimen or if the lesions are quite indurated or have extensive ulceration, an excisional biopsy may be needed. If melanoma is suspected, excisional biopsy is indicated. Any lesion on the vulva that is not known to be benign warrants a biopsy, and if there are multiple areas of abnormalities, multiple biopsies are indicated.

The goals of treatment for VIN are to prevent the development of invasive vulvar cancer and alleviate symptoms, without marked changes in the normal anatomy and function of the vulva. Treatment is individualized, with consideration of the biopsy results, location and extent of the disease, and the patient's symptoms. Observation suffices for VIN I. For patients with VIN II or VIN III, treatment usually is recommended, although observation is initially reasonable for women who have recently completed a course of corticosteroids, who are temporarily immunocompromised, or who are pregnant.

Management options currently include wide local excision, skinning vulvectomy, laser ablation, and topical treatment. Wide local excision or laser therapy for patients with no evidence of gross or microscopic invasion remains the primary treatment used for VIN. The surgical approaches for treatment appear to be similarly effective.[16] Treatment should go to a depth of 1 to 2 mm in non–hair-bearing areas and may need to extend to 3 mm in hair-bearing areas of the vulva in order to encompass any disease around the hair follicle. Disease-free margins of at least 1 cm should be excised around the lesion.

Topical agents that enhance or induce strong cell-mediated immune responses likely hold the greatest promise not only for control of HPV-related disease but also for reduction of future recurrences. Prior to the use of topical treatments, a careful colposcopic examination with biopsies must be done to rule out invasive disease. Topical 5% imiquimod acts by activating macrophages and dendritic cells to release interferon and other pro-inflammatory cytokines. These cytokines in turn lead to activation of the appropriate antigen-specific immune response. Imiquimod efficacy in the treatment of genital warts is well documented, and in a number of recent trials, its use has been associated with encouraging results in the treatment of VIN II and VIN III with a response rate approaching 90%.[15,18,19] Furthermore, van Seters found regression of VIN was associated with clearance of HPV.[19] Imiquimod has been associated with relief of pruritus and pain both immediately and for up to 12 months after use.[19] Side effects of imiquimod are usually local and may include mild to moderate erythema, erosion, burning, and ulceration.

Current treatments for VIN, although numerous, have largely resulted in suboptimal outcomes. Response rates have been poor and relapse rates high. Additionally, the resultant physical and psychological morbidity associated with treatment can be profound.

At least one-third of patients develop recurrent VIN regardless of the prior treatment modality. Risk factors for recurrence include immunosuppression, multifocal or multicentric disease, and positive margins on the biopsy specimen. For this reason, patients treated for VIN should be followed closely every 3 to 4 months until they are disease free for at least 2 years.

Vaginal Intraepithelial Neoplasm

Although the true incidence of vaginal intraepithelial neoplasm (VAIN) is not known, the diagnosis has been increasing over the last several years due to increased awareness, expanded cytologic screening, and more liberal use of colposcopy. The average patient is between 43 and 60 years of age. Infection with HPV is a common association.

VAIN is the terminology used to describe vaginal dysplasia. This spans the spectrum from VAIN I and II (only the lower one-third and two-thirds of the epithelium, respectively, is involved) to VAIN III (more than two-thirds of the epithelium is involved). Full-thickness involvement of the epithelium, or carcinoma in situ, is included under VAIN III. VAIN is consistently associated with prior or concurrent neoplasia elsewhere in the lower genital tract.

Premalignant neoplasms are almost always asymptomatic and are often detected by an abnormal Pap smear, although some patients may present with postcoital spotting or vaginal discharge. A tissue diagnosis must be established when an abnormal cytologic smear of the vaginal cuff is obtained. Colposcopy is performed with biopsy of the most abnormal area. If there is any question of invasion, excision under anesthesia must be undertaken. In postmenopausal patients, a few weeks of topical estrogen may help visualization and improve detection of VAIN.

After application of acetic acid, lesions often appear as raised or flat white, granular epithelium with well-defined borders; punctuation may or may not be present. Biopsies should be taken of any abnormal appearing areas. It may be helpful to slightly close the speculum prior to biopsy so the vaginal wall is not taut with tension, which makes performing a biopsy difficult. Local anesthetic (without epinephrine) should be used prior to biopsy. The choice of biopsy instrument depends on the type and location of the lesion. Sessile lesions may usually be biopsied with cervical biopsy forceps, whereas some raised lesions may be grasped with a forceps and affine scissors maybe sued for biopsy. The majority of lesions are in the upper one-third of the vagina, so in patients posthysterectomy, they may be difficult to see and skin hooks may be needed to evert areas of vaginal wall recess. If the surface is irregular or there are severe vascular abnormalities, an excisional biopsy should be taken to exclude an invasive process. Hemostasis can usually be obtained with ferric subsulfate (Monsel solution) or silver nitrate; in some cases, a suture may be necessary.

A variety of treatment options are available for VAIN: excision, ablation, topical chemotherapy, and radiation. Management should be individualized with consideration given to the presence of multifocal disease, any history of previous treatment failures, the woman's general health and risks from surgery, her desire to preserve her sexual function, and the degree to which the provider is sure that invasive disease has been ruled out. Some manage VAIN I with close surveillance. In general, surgical excision is the most common form of VAIN treatment. This may require local excision, partial vaginectomy, and rarely, total vaginectomy. Ablation is most commonly done with the CO_2 laser, and up to one-third of patients may need more than one treatment. There are no guidelines clearly defining the ideal topical treatment for multifocal high-grade VAIN, although it appears to

be appropriate first-line therapy for women with early lesions and multifocal disease or those who are poor surgical candidates. Imiquimod and 5-fluorouracil are the topical agents most commonly used. Radiation therapy is reserved for patients who have failed previous treatments for VAIN; are poor surgical candidates; or have extensive, multifocal disease. Because VAIN is usually multifocal, follow-up every 6 months for up to 2 years and then annually thereafter is warranted.

Extramammary Paget Disease

Extramammary Paget disease is an uncommon lesion that arises in skin rich in apocrine glands, with limited information based on case reports and case series owning to its rarity. Vulvar Paget disease is most often an apocrine carcinoma in situ. However, 4% of women will have a contiguous adenocarcinoma and up to 26% will have noncontiguous underlying adenocarcinoma.[20,21] Patients characteristically present with symptoms including burning or itching, with a reported age range of 47 to 93 years in one case series.[22] The classic appearance of vulvar Paget disease is a red velvety plaque, which may be mistaken for vulvar eczema (Fig. 14.7).

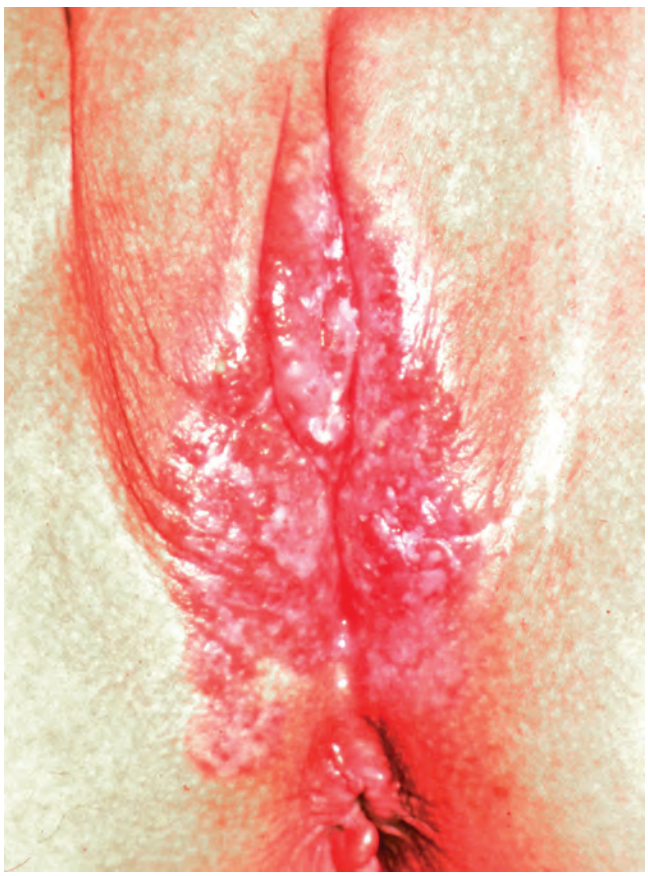

FIGURE 14.7 Paget disease of the vulva. The lesion is red, moist, and sharply demarcated. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.)

It is usually multifocal and may occur anywhere on the vulva, mons, perineum/perianal area, or inner thigh. Vulvar biopsy should be performed in patients with suspicious lesions, including those with persistent pruritic eczematous lesions that fail to resolve within 6 weeks of appropriate antieczema therapy.

Paget disease is diagnosed by histologic appearance including the presence of signet-ring or Paget cells. Following biopsy confirmation of vulvar Paget disease, patients should be screened for possible associated or synchronous cancers with pelvic exam, cervical cytology, endometrial biopsy, and mammography, as well as targeted evaluation for anal (occult blood testing, endoscopy) or urethral (urine cytology, cystoscopy) lesion involvement given the risk for underlying adenocarcinoma.[22]

Treatment of noninvasive Paget disease is classically by surgical excision with limited evidence for nonexcisional treatment modalities such as laser ablation, radiotherapy, photodynamic therapy, and imiquimod. The risk of recurrence following excision is reported to occur in up to 60% of women regardless of margin status or extent of surgery and is attributed to the presence of "skip lesions."[22] The use of frozen section to ensure complete excision (negative margin status) has been employed to reduce the high rate of recurrence without clear benefit. Given the risk of recurrence and progression to invasive disease, long-term monitoring with biopsy of any abnormal vulvar lesion is paramount in patients with a history of Paget disease.

VULVAR DERMATITIS

The term dermatitis (or eczema) describes a poorly demarcated, erythematous, and usually itchy rash. Burning can sometimes occur in cases of mucosal involvement. Subtypes are numerous and can be classified as either exogenous (irritant or allergic contact dermatitis) or endogenous (atopic dermatitis). Endogenous or atopic dermatitis has a familial predisposition and may begin in childhood.

Dermatitis is common and has been reported to occur in 20 to over 60% of patients seen with chronic vulvar symptoms, with atopic dermatitis being by far the most frequently encountered.[23] Unfortunately, the clinical appearance of the vulva often does not help secure the diagnosis, and in many cases, more than one process has led to the symptoms the patient reports. It is not uncommon to see a mixed picture where endogenous dermatitis or another epithelial disorder has been worsened by use of ointments or creams to which the patient has adversely reacted.[23,24] Vulvar dermatitis often presents as chronic irritation and/or pruritus (that is often nocturnal), and patients report persistent rubbing and itching to alleviate the symptoms. The symptoms may be worsened by stress, menstruation, heat, or sweat. Chronic scratching or rubbing by the patient may lead

to histologic changes in the dermis referred to as squamous hyperplasia or lichen simplex chronicus.

Allergens, Irritants, and Contact Dermatitis

Contact dermatitis is one of the most frequently encountered and often simultaneously avoidable problems seen in vulvar specialty clinics with a reported prevalence of up to 54% in vulvar clinic patients.[25] The susceptibility of the vulvar skin to inflammation is widely underestimated by patients as well as providers. Compared to other areas of exposed skin, the stratum corneum of the vulva functions less efficiently as a barrier, which increases its susceptibility to irritants. Many seemingly innocuous behaviors, such as bathing, the use of sanitary or incontinence pads, or exposure to known irritants or allergens in numerous topical medications, have the potential to initiate this eczematous process.[24] Active and inert components of topical medications are a very common cause of allergic vulvar dermatitis. Latex sensitivity or reactions to proteins in seminal plasma are infrequent causes.[26] It is important to remember that a patient may have used an agent for months or years without any problem and then have an "allergy" develop. Additionally, self-treatment (using over-the-counter agents or alternative therapies) often exacerbate the process prior to medical evaluation.

Irritant contact dermatitis has been identified in up to 26% of women diagnosed with vulvar dermatitis, often as a result of exposure to such irritants as detergents; soaps; perfumes; semen; and propylene glycol, an additive found in many topical medications. Allergic contact dermatitis, in contrast, is an immunologically mediated inflammatory reaction (type IV delayed hypersensitivity) to an allergen in a previously sensitized woman. Although distinguishing allergic from irritant contact dermatitis can be difficult, the intermittent nature of the symptoms and the timing of symptom onset (10 to 14 days following exposure but may be less than 24 hours if already sensitized) serve as important keys to making the diagnosis of the former. The list of commonly encountered allergens, although similar to that of common irritants, also includes a variety of topical medications such as antibiotics (e.g., neomycin, bacitracin), antifungals (clotrimazole, miconazole), all corticosteroids, and the greatest offenders, the topical anesthetics.[24] Additionally, close questioning of the patient's personal practices is an important way to detect potential irritants and/or allergens as well as unhealthy vulvar hygiene habits. In one study, over 60% of women attending a specialty clinic for vulvar disease described personal hygiene and/or self-treatment practices that may contribute to vulvar dermatitis.[26]

The presence of contact hypersensitivity in an underlying vulvar dermatitis should be suspected in cases where a patient does not respond following therapy or experiences a recurrence of symptoms after initial remission.[25] In this case, patch testing may be beneficial. Not only will patch testing help to distinguish between atopic and contact dermatitis, it may help determine the cause of the dermatitis. There is a standard patch test series in the United States that tests for the most common and important allergens in North America. Positive patch tests for relevant substances occur in 25 to 60% of women with vulvar pruritus.[27]

On examination, clinical signs can range from mild erythema, swelling, and scaling to marked erythema, fissures, edema, and vesicles or bullae. Chronic eczema is often erythematous and scaly (Fig. 14.8). Secondary infection may be present as well. Confirmation of the diagnosis should include assessment to rule out candidiasis. Biopsy, which will show nonspecific changes such as spongiosis, parakeratosis, and some dermal inflammatory infiltrate, is not helpful.

Treatment consists of removal of the offending agent or practice, correction of barrier function, elimination of scratching, and reduction of inflammation. Barrier function should be restored through the use of Sitz baths, estrogen therapy if indicated, treatment of concomitant

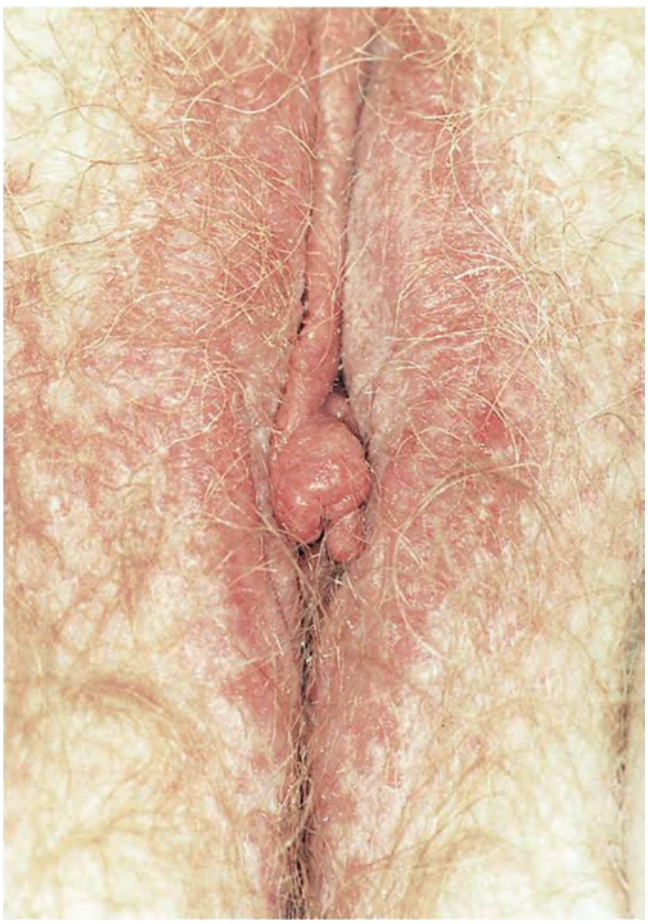

FIGURE 14.8 Moderate erythema in patient who complains of pruritus for 3 years. Clinical impression was eczema, and patient was advised to use hypoallergenic soap. Condition resolved. (From Wilkinson EJ, Stone IK, eds. *Atlas of Vulvar Disease*. Baltimore: Lippincott Williams & Wilkins; 1995:81, with permission.)

infection if present, and application of a thin layer of plain petrolatum. Exposing the vulva to warm water, without any additives, for at least 5 minutes in the morning and again at night, helps to rehydrate the skin and soothe the sensory nerve endings of the vulva. The moisture may be sealed in with a topical corticosteroid ointment. Medications with antihistamine and sedative properties, such as doxepin or hydroxyzine (10 to 50 mg in the evening), can be added to control nocturnal itching, whereas a selective serotonin reuptake inhibitor (SSRI) can be used during the day. Nonsedating antihistamines do not help with vulvar pruritus. Anti-inflammatory therapy should also begin with a mid- to high-potency corticosteroid for 2 to 3 weeks (Table 14.2). A weaker corticosteroid, such as 1% hydrocortisone, can then be continued as needed. There is no evidence that application of topical corticosteroids more than once daily is beneficial.[28]

In recalcitrant cases, oral or intramuscular (IM) corticosteroids may be necessary.[24] IM triamcinolone 60 mg may be given IM every 6 weeks for up to three doses. After the first injection, petrolatum jelly may be used twice a day after sitz baths for 2 weeks followed by use of a superpotent topical corticosteroid. Use of IM triamcinolone may cause hyperglycemia, changes in menstruation, and adrenal suppression. It should not be used in women with a history of either severe depression or bipolar disease.

An intralesional injection of triamcinolone acetonide 3.3 to 10 mg/mL may also be tried in resistant cases. A total of 1 to 2 mL is given by injecting small amounts throughout the entire lesion or plaque; this may be repeated monthly up to three times. It may be helpful to apply a topical anesthetic such as EMLA prior to injection.

Lichen Simplex Chronicus

Vulvar lichen simplex chronicus, also known as squamous hyperplasia, is a common, chronic eczematous disease characterized by intense and unrelenting itching and scratching. In vulvar specialty clinics, lichen simplex chronicus accounts for 10 to 35% of patients evaluated. Although lichen simplex chronicus occurs primarily in middle to late adult life, it can occur in children. Up to 65 to 75% of patients will report a history of atopic disease (hay fever, asthma, childhood eczema), and as such, lichen simplex chronicus can be seen as a localized variant of atopic dermatitis. Patients often present with intractable itching and pruritus, and most will admit to vigorous scratching or rubbing. The pruritus is often worse at night, and chronic scratching may lead to lichenification, fissures, and postinflammatory pigment changes. Thus, lichen simplex chronicus represents an end-stage response to a wide variety of possible initiating processes, including environmental factors (e.g., heat, excessive sweating, and irritation from clothing or topically applied products) and dermatologic disease (e.g., candidiasis, lichen sclerosus).[29,30]

Clinically, lichen simplex chronicus appears as one or more erythematous, scaling, lichenified plaques (Fig. 14.9). Various degrees of excoriation are often visible. In long-standing disease, the skin appears thickened and leathery, and areas of hyperpigmentation and hypopigmentation may be present. Erosions and ulcers can also develop, most commonly from chronic scratching. Vaginal fungal cultures are helpful in determining the presence of an underlying condition on which lichen simplex chronicus is superimposed. Biopsy (which would demonstrate marked hyperkeratosis with widening and deepening of the rete ridges) is rarely necessary unless an underlying disease (such as lichen sclerosus or psoriasis) is suspected or the patient fails to respond to treatment.

Treatment consists of identification and removal of the initiating factor, repair of the skin's barrier layer function, reduction of inflammation, and disruption of

TABLE 14.2 Common Topical Steroids

Topical Steroid Class	Name (Trade)	Name (Generic)	Common Uses
Class I Super-potent	Temovate (0.05% cream, ointment)[a] Ultravate (0.05% cream, ointment)	Clobetasol propionate Halobetasol propionate	Lichen sclerosus Lichen planus
Class II High potency	Lidex (0.05%)	Fluocinonide	Psoriasis Lichen simplex chronicus
Class III	Valisone (0.1% ointment)	Betamethasone valerate	
Class IV Midpotency	Kenalog (0.1% cream) Westcort (0.2% ointment)	Triamcinolone Hydrocortisone valerate	Eczema Mild irritation
Class V	Locoid (0.1% cream) Valisone (0.1% cream) Westcort (0.2% cream)	Hydrocortisone butyrate Betamethasone valerate Hydrocortisone valerate	
Class VII Mild	Hydrocortisone 1.0%, 2.5%	Hydrocortisone	Mild eczema Maintenance

[a]Creams tend to work better in the vagina due to better absorption. Ointments work well on the vulva because they are less irritating than creams, solutions, jelly, or lotions and provide a soothing barrier.

Data from Ference JD, Last AR. Choosing topical corticosteroids. *Am Fam Physician*. 2009;79(2):135–140.

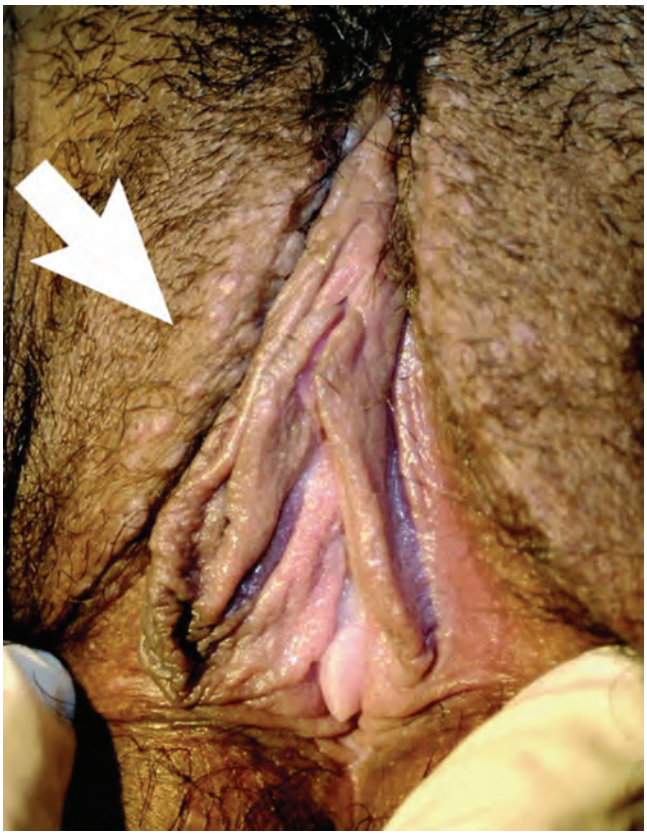

FIGURE 14.9 Mild lichen simplex chronicus. Note the subtle lichenification (thickening) on the labia majora bilaterally (*arrow*). (From Boardman LA, Botte J, Kennedy CM. Recurrent vulvar itching. *Obstet Gynecol*. 2005;105[6]: 1451–1455.)

the itch–scratch cycle. Mid- to high-potency topical corticosteroids (depending on the presence of underlying disease) should be applied nightly until symptoms begin to abate; less frequent use (e.g., alternate nights, then twice weekly) should continue until the condition resolves. As noted previously, medications with antihistamine and sedative properties can be added to control nocturnal itching; an SSRI for daytime use and oral or intralesional steroids can be used for refractory cases. Given the side effects of local steroid therapy, calcineurin inhibitors tacrolimus (0.03% ointment) and pimecrolimus (1% cream) may be considered in refractory cases and have been approved as second-line anti-inflammatory agents for the treatment of dermatitis.[31] These are used sparingly twice a day for 14 to 30 days followed by maintenance therapy twice a week. Upon discontinuation, the dermatitis recurs in 35 to 54% of patients. The use of tacrolimus may cause burning or stinging and these side effects may be minimized through the application of a film of petrolatum jelly prior to use of the ointment.

Seborrheic Dermatitis

Seborrheic dermatitis is very rare on the vulva, and its etiology is not known. It usually affects the scalp, face, presternal, and intrascapular areas (areas rich in sebaceous glands). Lesions are pale to yellowish red, with greasy, nonadherent scales and are not clearly defined. Secondary infection may occur. Vulvar lesions are usually distributed symmetrically on the mons pubis and genitocrural folds where sebaceous glands are concentrated; involvement of labia minora is rare.

Clinically, seborrhea may be confused with psoriasis, candidiasis, tinea cruris, or lichen simplex chronicus. The diagnosis is one of exclusion. When present in the genital region, there will often be seborrheic dermatitis involving other areas of the body.

Initial treatment consists of low- to high-potency corticosteroid ointment as a burst and taper with or without a topical antifungal such as ketoconazole.[29] If topical steroids are not adequate in controlling symptoms, further treatment considerations may include selenium sulfide, salicylic acid, and tar shampoo. However, the use of these agents may be limited by contact irritation to sensitive vulvar skin.

Hidradenitis Suppurativa

Hidradenitis suppurativa, also termed acne inversa and Verneuil disease, is a common chronic, suppurative, cutaneous process that results from occlusion of follicles. It commonly involves the intertriginous skin of the axillary, groin, perineal, perianal, and inframammary regions (Figs. 14.10 and 14.11). Scarring of the affected sites results from chronic infection and draining abscesses.

The prevalence of hidradenitis suppurativa is estimated to be as high as 4%, although hidradenitis suppurativa is often underrecognized and underdiagnosed.[32,33] Women are more likely to be affected than men by a ratio of about 3:1. Smoking seems to be a major triggering factor. Other causal factors may include both acquired and genetic characteristics including onset after puberty and prior to age 40 years, obesity (with hyperandrogenism),

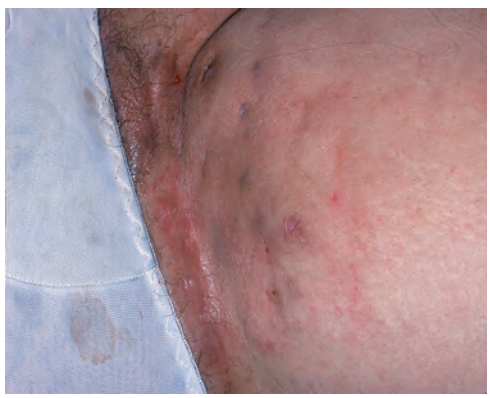

FIGURE 14.10 Hidradenitis suppurativa. This patient has involvement of the inguinal areas, labia majora, and mesial thighs. Her undergarment was stained by the oozing lesions. (From Goodheart HP, MD. *Goodheart's Photoguide of Common Skin Disorders*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003.)

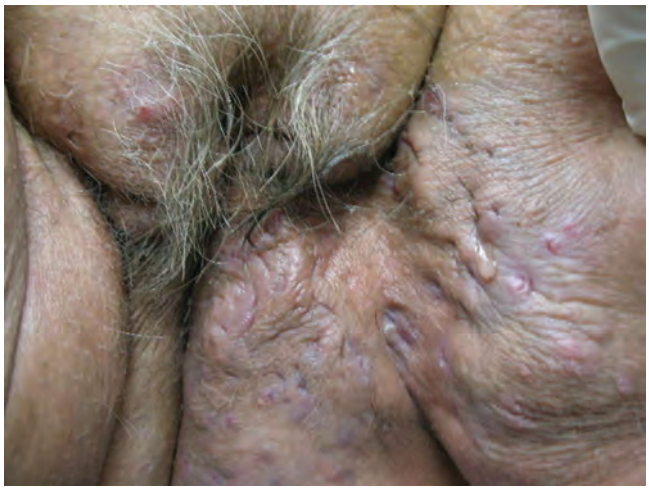

FIGURE 14.11 Hidradenitis suppurativa. (Note scarring, pitting, and multiple fistulous tracts.) (From C. K. Stockdale personal library.)

TABLE 14.3 Hurley's Clinical Staging

The severity of HS can be classified according to the Hurley's stage, which correlates with the extent of treatment that is likely to be needed.

- Stage I—Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring). Although classically managed with drug therapy, hormonal and metabolic controls are now part of the treatment.
- Stage II—Recurrent abscesses with tract formation and cicatrization. Single or multiple widely separated lesions. Managed with drug therapy and limited excision of recalcitrant lesions. Unroofing is emerging as the preferred technique.
- Stage III—Diffuse or near diffuse involvement, or multiple interconnected tracts and abscesses across the entire area. Unlikely to benefit from medical therapy alone; wide surgical excision (either unroofing or en bloc excision) is recommended either as adjunctive or curative therapy.

HS, hidradenitis suppurativa.
From Hurley, HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach. In: Roenigk RK, Roenigk HH, eds. *Dermatologic Surgery*. New York: Marcel Dekker; 1989:729.

association with other endocrine disorders (e.g., diabetes), and an apparent familial predisposition in some patients. Axillary and inguinal involvement is more common in females, whereas perianal and buttocks involvement is more common in males.[33]

The onset of hidradenitis suppurativa is insidious. Early diagnosis of hidradenitis suppurativa is easily overlooked and often attributed to simple comedones of acne. However, unlike acne, significant sebaceous gland involvement is not a component of hidradenitis suppurativa. Early symptoms consist of pruritus, erythema, burning, and local hyperhidrosis.[34] Occlusion of a hair follicle results in a cyst, similar to the comedones of acne. The follicular duct expands and eventually ruptures, which release a number of antigens and other inflammatory stimuli that cause the development of an acute inflammatory response in the surrounding tissue. Epithelial cells from the follicular wall, as well as stem cells, are released during the rupture as well and may promote cellular proliferation. The combination of acute inflammation and cellular proliferation is thought to cause the formation and spread of dermal and subcutaneous abscesses and sinus tracts that are seen with hidradenitis suppurativa. Lesions are extremely painful, and the average duration of a lesion is 7 days. Most patients have at least one active lesion at any given time. As the area heals, it becomes scarred and fibrotic. Chronic lymphedema may develop as a result of lymphatic destruction. Ultimately, hyperpigmentation, scarring, pitting, and multiple fistulous sites are noted.

Although specific diagnostic criteria do not exist, the diagnosis becomes apparent with disease progression; biopsy is neither required nor diagnostic. Clinical criteria suggesting hidradenitis suppurativa include recurrent deep boils for more than 6 months in flexural apocrine gland skin sites (typically involving the axilla, inguinal, and anogenital areas), onset after puberty, poor response to conventional antibiotics, and tendency toward relapse and recurrence.[35] Late disease is characterized by chronic infection, draining abscesses, nodules, sinus tracts, scarring, and hyperpigmentation. Hidradenitis is graded according to Hurley's clinical staging system or the more recently developed modified Hidradenitis Suppurativa Score (Tables 14.3 and 14.4). The severity of hidradenitis suppurativa can be classified according to the Hurley's stage, which correlates with the extent of

TABLE 14.4 Modified Hidradenitis Suppurativa Score

Characteristics of Hidradenitis Suppurativa Lesions	Points per Lesion
Anatomic region	
Any	3
None	0
Types of lesions	
Fistula	4
Nodule	2
Abscess	1
Scar	1
Other	1
Total area involved[a]	
<5 cm	2
5–10 cm	4
>10 cm	8
Are all lesions clearly separated by normal skin?	
Yes	0
No	6
Total score:	

The Hidradenitis Suppurative Score (HSS) as modified by Sartorius was proposed to standardize comparative analyses of treatment for HS.
[a]Record the longest distance between two relevant lesions (e.g., nodule and fistula) in each affected region, or record the size of a single lesion in each affected region.
Data from Sartorius K, Lapins J, Emtestam L, et al. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. *Br J Dermatol*. 2003;149:211; Mahmoud BH, Tierney E, Hexsel CL, et al. Prospective controlled clinical and histopathologic study of hidradenitis suppurativa treated with the long-pulsed neodymium:yttrium-aluminium-garnet laser. *J Am Acad Dermatol*. 2010;62:637–645.

treatment that is likely to be needed. The modified score includes the anatomic region affected by the disease, the number and characteristics of lesions, the longest distance between two relevant lesions, and the presence of normal skin bridges between lesions.

The differential diagnosis of hidradenitis suppurativa includes Crohn disease, follicular pyoderma, acne vulgaris, and Fox-Fordyce disease. Finally, SCC arising in hidradenitis suppurativa is rare but has been reported. Thus, although biopsy is not indicated for the diagnosis of hidradenitis suppurativa, it is indicated when there is concern for malignancy.

Treatment of hidradenitis suppurativa is challenging and based primarily on anecdotal evidence (Table 14.5). Patients need to be assured that the disease is not contagious nor is it due to poor hygiene. Current treatment is directed at prevention of new lesions through medical management and elimination of existing lesions surgically when appropriate. Smoking cessation is imperative. In order to improve the local environment, avoidance of irritants, heat, sweating, and reducing friction (e.g., avoidance of tight clothing, limit pad use) is encouraged. Additionally, weight reduction is often helpful. The use of washcloths should be discouraged as should high-pH soaps, whereas the use of clean bare hands for cleansing affected areas and neutral-pH detergents may be encouraged. Overall, treatments including oral antibiotics, topical clindamycin, isotretinoin, systemic and intralesional corticosteroids, and surgery have been inconsistently effective. There is no data to support the use of one medical therapeutic approach over another.

Antibiotics are used primarily for their anti-inflammatory properties and routine cultures and sensitivities are not recommended. If taken within an hour or two of prodromal symptoms, antibiotic use may help stop the evolution of a nodule to an abscess, especially in patients with only a few outbreaks a year. There is no evidence that long-term antibiotics alter the natural history of the disease. Relapse is almost inevitable after the antibiotics are stopped unless the foreign body reaction induced by the follicular duct wall rupture and ensuing inflammatory response are eliminated. The use of topical clindamycin (1% lotion twice a day for 1 to 3 months) or tetracycline (500 mg twice a day for 3 months) has been shown to

TABLE 14.5 Treatment of Hidradenitis Suppurativa

Treatment of Hurley's Stage I Medical Therapy

- Antibiotics and intralesional steroids to suppress inflammation. For oral antibiotics, use doxycycline 50 mg daily; recommended topical antibiotic (clindamycin 1% lotion twice a day). Intralesional steroid recommendation: triamcinolone acetonide (5 to 10 mg/mL, 0.1 to 0.5 mL injected into the center of individual, painful, early papules/small nodules with a 30-gauge needle once monthly for one to three injections).
- For resistant cases, trial of oral systemic antibiotics. Options include a 7- to 10-day course of tetracycline (250 to 500 mg four times daily), doxycycline (100 mg twice daily), clindamycin (300 mg twice daily), or amoxicillin/clavulanate (500 mg to 1 g every 8 hours).
- Consider concurrent therapy with antiandrogens. Options include ethinyl estradiol/drospirenone oral contraceptive alone or supplemented with spironolactone (starting at 25 mg daily and increasing to 100 mg/day).
- Zinc gluconate (50 to 90 mg orally daily) to help prevent development of new or recurrent lesions. This is a new treatment approach and should be started at first diagnosis in all stages.

Treatment of Hurley's Stage II. Combined medical and surgical therapy. The aim in stage II is to reduce the activity to stage I disease.

- Stage II involves the same baseline treatments as stage I.
- For patients with little scarring but a lot of inflammation, use the antibiotics listed above; for more severe disease, oral rifampin (rifampicin) (300 mg twice daily) and clindamycin (300 mg twice daily) may be used for 3 months. For patients who respond poorly to antibiotics, avlosulfone (Dapsone) 50 to 100 mg daily can be used, and prednisone can be considered for acute inflammatory nodules, as above.
- Surgically unroof persistent chronic sinus tracts and cysts to unroof in lieu of excision to avoid the morbidity of extensive surgery while bringing symptoms under control.
- The only indication for simple incision and drainage is relief of pain from a tense abscess. Concurrent antibiotics are given: amoxicillin-clavulanate 3 g in a single dose, then 1 g orally three times daily for 5 to 7 days following the drainage.
- Postoperatively, switch the patient to a maintenance regimen of an antibiotic such as doxycycline (doxycycline 100 to 200 mg daily) or dapsone (100 mg daily). Continue zinc gluconate (50 to 90 mg daily) and antiandrogens, as above. A dairy product free diet is strongly advised.

Treatment of Hurley Stage III. The aim in stage III is to reduce the activity to stage II and eventually stage I disease.

- Stage III involves the same baseline treatments as stage I and stage II.
- Consider surgical intervention for stage III disease with concurrent medical treatment to facilitate the surgical procedure and as prophylaxis against development of future lesions. Medical therapy reduces inflammation and helps to clearly define the lesions.
- Use an anti-inflammatory agent prior to surgery. Options include prednisone (1 mg/kg/day orally to start), cyclosporine (4 to 5 mg/kg/day orally), or a TNF-alpha inhibitor (e.g., infliximab 5 mg/kg intravenously every 6 weeks), or T-cell inhibitors, which should only be prescribed by a physician experienced in the use of these drugs. We also suggest concurrent antibiotic therapy, for example, clindamycin (300 mg orally twice daily) with rifampicin (300 mg orally twice daily).
- Wide surgical unroofing and debriding of all cysts and sinuses and fistulous tissue should be done only by an experienced surgeon. Healing can be by secondary intention or may be accelerated with mesh grafting. Primary closure is best avoided in active disease to avoid burying residual proliferative inflammatory foci of activity. Such residual activity will surface and spontaneously heal if healing by secondary intention is permitted. At times, skin flaps may be required, but this is unusual and also risks burying disease activity. Although re-excisions are likely to be required with this approach, these procedures will involve smaller areas that may be appropriate for primary closure later with a reasonable healing time.
- Postoperatively, switch the patient to a maintenance regimen of antibiotic, such as doxycycline (doxycycline 100 to 200 mg daily) or dapsone (100 mg daily). Continue zinc gluconate (50 to 90 mg daily) and antiandrogens. A dairy product free diet is strongly advised.

Data from Margesson LJ, Danby FW. Treatment of hidradenitis suppurativa. UpToDate Web site. http://www.uptodate.com/contents/treatment-of-hidradenitis-suppurativa?detectedLanguage=en&source=search_result&search=hidradenitis+suppurativa&selectedTitle=1~33&provider=noProvider. Accessed December 2, 2013.

decrease abscess formation, leading to fewer inflammatory nodules and pustules.[36,37] Other antibiotics that have been used include dicloxacillin, erythromycin, minocycline, cephalosporins, and dapsone (100 mg daily).[38]

For mild hidradenitis suppurativa, both intralesional triamcinolone acetate (5 to 10 mg/mL using 0.1 to 0.5 mL every month for up to 3 months) and low-dose isotretinoin (20 mg/day) have demonstrated some efficacy in early isolated lesions and appear to be helpful in the prevention of new lesions. The use of intralesional steroids is not appropriate for patients with extensive disease. Women using isotretinoin must be on adequate contraception because it is teratogenic; oral contraceptives with low androgenic progestins are recommended if possible because they may also help prevent recurrent lesions. Treatment with antiandrogens has produced mixed results in women with hidradenitis suppurativa.[39,40] Although there are no conclusive studies regarding diet and hidradenitis suppurativa, anecdotal experience suggests that the use of a nondairy diet with or without low glycemic load diet may help some patients.

Treatment of late stage hidradenitis suppurativa is very difficult. The use of cyclosporine, infliximab (tumor necrosis factor [TNF]-alpha inhibitor infusion), T-cell specific agents, and aggressive hormonal and dietary changes have helped in small numbers of patients with moderate improvement and significant side effects.[41-44]

Although surgery is heralded as the primary treatment of severe, extensive hidradenitis suppurativa, all treatment options are noted to have a high recurrence rate, including radical surgery. Simple incision and drainage of individual nodules may be undertaken to provide short-term pain relief, but there is no long-term benefit to this approach because lesions will recur. Further surgical options include unroofing of sinus and fistulous tracts, local excision, and wide excision (with or without skin grafting). Thus, the extent of excision should be individualized based on the desired outcome as well as the stage and location of disease.

VULVAR DERMATOSES

Vulvar dermatoses are skin disorders that often cause itching, burning, and discomfort. The most common vulvar dermatoses include "the three lichens": lichen simplex chronicus (discussed previously), lichen sclerosus, and lichen planus (LP). Although they are discussed separately, they may coexist simultaneously.

Lichen Sclerosus

Lichen sclerosus (LS), a chronic disorder of the skin, most commonly affects the vulva, with extragenital lesions reported in 5 to 15% of patients. Patients presenting with LS most commonly complain of pruritus, followed by irritation, burning, dyspareunia, and tearing. LS may affect any age group. However, there is a bimodal age peak with the mean age of onset in the fifth to sixth decade and a childhood variant occurring in prepubertal girls. Although the etiology remains unclear, an autoimmune process or possible genetic link is likely. Associations between LS and a variety of autoimmune-related disorders including alopecia, vitiligo, thyrotoxicosis, hypothyroidism, and pernicious anemia have been identified.[45,46] Additionally, LS is associated with an increased risk (4 to 5%) of SCC of the vulva.[45] For this reason, patients with vulvar LS should be examined at least yearly with biopsies taken of any suspicious areas and women should be encouraged to do monthly self-exams as well. Although a hormonal association has been postulated for LS because the highest incidence in women is observed during physiologically low estrogen states, no association has been found between the condition and pregnancy, contraceptive use, or postmenopausal hormone therapy.[47]

Despite the association between LS and autoimmune-related disorders, there are no recommendations regarding evaluation for coexisting autoimmune-related disorders in women diagnosed with LS beyond a brief examination for alopecia areata and vitiligo and consideration of thyroid function tests.

The major symptoms of vulvar LS are intense pruritus that may be of such intensity it interrupts sleep patterns. It may also be associated with pruritus ani, painful defecation, rectal bleeding, and anal fissures. Fusion of tissues over the clitoris may decrease sexual sensation; dyspareunia may also occur. For some women, a dull discomfort is the prodromal symptoms of the gross lesions. LS may also be completely asymptomatic but still lead to skin changes, scarring, and loss of normal architecture.

On examination, typical lesions of LS are porcelain-white papules and plaques, often with areas of ecchymosis or purpura. The skin commonly appears thinned, whitened, and crinkling (hence the description, "cigarette paper") (Fig. 14.12). Variations in presentation do occur however, and lesions may range be hemorrhagic, purpuric, hyperkeratotic, bullous, eroded, or ulcerated.[48] Lesions most often involve the labia minora and/or labia majora, although the whitening of the skin may extend over the perineum and around the anus. Fissuring is often seen by the clitoris, in the interlabial folds, or perianally. This perianal involvement can create the classic "figure of eight" or hourglass shape. Chronic scratching may result in excoriations or lichenification of the skin (thickening of the epidermis with exaggeration of normal skin lines). Over time, there is atrophy of the involved tissues and a loss of vulvar architecture, with complete flattening of the skin folds. Although the vagina is spared with LS, involvement of the mucocutaneous junctions may cause scarring and narrowing of the introitus. Other findings include fusion of the labia minora, phimosis of the clitoral hood, and fissures.[46,49] Because other vulvar diseases can mimic LS (such as LP, vitiligo, cicatricial pemphigoid, and psoriasis), at least a 3-mm punch biopsy is necessary to confirm the diagnosis

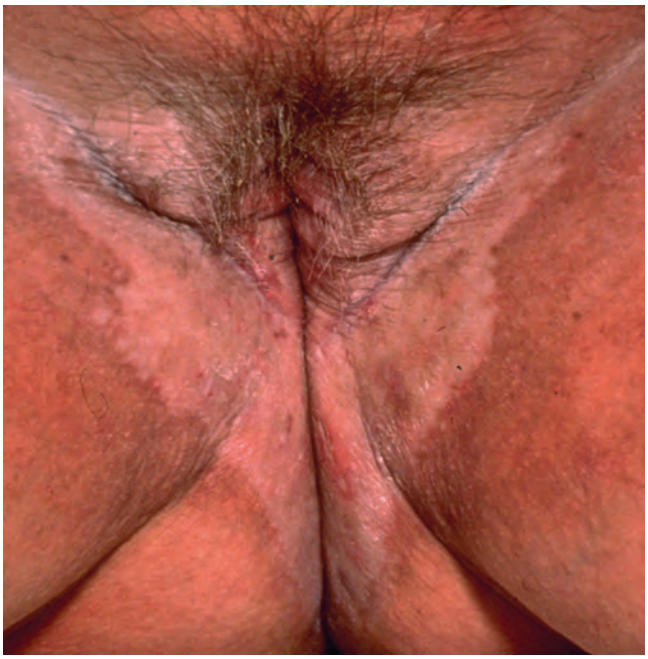

FIGURE 14.12 Lichen sclerosus of vulva. The sharply demarcated white lesion affects the vulva and perineum. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.)

especially with early onset. Because the differential diagnosis is so broad, empiric therapy before biopsy-proven diagnosis is not recommended. Women with vulvar LS are at increased risk of developing squamous cell cancer of the vulva (4 to 5%).[50]

There is no universal approach to management of LS, and treatment is done primarily to relieve pruritus and pain, although there is evidence that distortion may be prevented if treatment is initiated early on in the disease.[51] The likelihood of improvement or remission may be higher in older women.[52] The recommended treatment for LS is a high-potency topical steroid, the most studied of which is clobetasol propionate.[53,54] Although there are no randomized controlled trials to provide evidence regarding the most effective steroid regimen, a reasonable approach is to begin with once daily application for 6 to 12 weeks. Some advocate discontinuation of therapy following the initial regimen with use of therapy for flares or recurrent symptoms, whereas others recommend an ongoing maintenance regimen of once-weekly application of either an ultrapotent or moderate-strength steroid.[46] Ointments are preferable to creams, which may contain irritants. Patients may need to apply the ointment with a mirror to ensure it is placed properly, and it is important to stress that only a thin layer needs to be applied. In patients with a partial response to treatment yet continue to have burning, irritation, or pain, it may be necessary to rule out other concomitant conditions such as superinfection or candidiasis and treat these conditions if found. In patients with resolution of the pruritus and skin lesions but for whom pain persists, a diagnosis of vulvodynia should be considered.

About 95% of patients will achieve complete or partial relief of symptoms and resolution of some physical changes, although if whitening, atrophy, and scarring are present, these changes will not reverse with treatment.[55] Initially, monitoring at 3 and 6 months following initial therapy is recommended to assess the response to therapy, monitor for steroid-related problems in the surrounding skin as well as the treated skin, adjust the frequency of corticosteroid application, and ensure proper application of the medication. For patients who do not want to take maintenance therapy, examinations should be done every 3 to 6 months because recurrences may be asymptomatic but permanent scarring and/or atrophy associated with recurrences may occur over a relatively short period of time.

In cases with thickened, hypertrophic plaques, response to topical steroids may be poor, and in these instances, intralesional injection of triamcinolone hexacetonide (5 to 20 mg) monthly for 3 months may help resolve these lesions. Pretreatment with a topical anesthetic such as lidocaine/prilocaine cream and use of a small (25 to 30 gauge) needle will help minimize pain resulting from the injection(s).

As identified for the treatment of other dermatoses, the use of calcineurin inhibitors such as tacrolimus and pimecrolimus have been evaluated in the treatment of LS to reduce the potential complications of ultrapotent steroid therapy.[56] Unlike high-potency steroids, macrolide immunosuppressants do not affect collagen synthesis, so they do not cause thinning of the dermis. Tacrolimus burns on application and is often discontinued by patients for this reason. In instances where there is fissuring that has not responded to high-potency steroids, the use of tacrolimus 0.03% twice a day for a month, followed by re-evaluation, may show a response. Application of petrolatum or clobetasol first may help prevent the burning associated with tacrolimus.

Although promising as therapies for some vulvar conditions, including LS, subsequent reports of a possible link to skin cancer and lymphoma based on animal studies and case reports in humans limit the use of this medication. Subsequently, the FDA issued a "black box" warning regarding these concerns. For this reason, it is recommended that providers use the topical immunosuppressant calcineurin inhibitors, of which tacrolimus is one, as second-line agents for short-term and intermittent treatment in patients unresponsive to, or intolerant of, other treatments.

Surgery, although not curative, is reserved for the treatment of malignancy and postinflammatory sequelae (e.g., release of labial adhesions). Surgical approaches should be deferred until after treatment with medication because it may exacerbate symptoms or irritate and exacerbate symptoms. Excisional surgery with skin grafting is not curative because the disease recurs in the skin graft that is applied. Introital stenosis, posterior fissuring, and scarring at the fourchette can be treated by vulvoperineoplasty with use of part of the vaginal wall

in the repair because vaginal tissue is not affected by LS.[57] Adhesions burying the clitoris can result in formation of painful pseudocysts and may need surgical repair.[58,59] Finally, treatment with other topical therapies, including testosterone and progesterone, has inconsistently resulted in improvement in LS and therefore are not currently recommended. Indications for referral to a specialist for treatment of LS are listed in Table 14.6.

It is extremely important to counsel patients about the chronicity of LS, the frequent recurrences and remission of signs and symptoms, and assurances that the condition is manageable. A review of good vulvar hygiene is helpful as well emphasizing the need to stop scratching.

Psoriasis

Psoriasis is a chronic papulosquamous disorder occurring in 2 to 3% of the population, which can frequently affect the genital skin. There seem to be two peaks in age of onset: between the ages of 20 and 30 years and between the ages of 50 and 60 years. About one-third of patients with psoriasis have a family history of the disease. However, vulvar psoriasis, which is usually pruritic, can be seen in girls and women of all ages. Smoking is associated with an increased risk of psoriasis and with increased severity of psoriasis.[60] Obesity and a higher body mass index (BMI) may also increase the risk of psoriasis.[61] Psoriasis is a complex immune-mediated disease, and the primary insult that initiates psoriasis is not always clear. Patients with psoriasis have a higher frequency of metabolic syndrome, cardiovascular disease, inflammatory bowel disease, and cancer.[62]

Psoriasis may present anywhere on the body although it typically presents on extensor surfaces, the trunk, or scalp. When it appears on intertriginous areas, such as the inguinal, perineal, genital, intergluteal, axillary, and inframammary regions, it is referred to as inverse psoriasis. The typical clinical features of psoriasis are well-demarcated, symmetric "salmon pink" plaques, which contain silvery scales (Fig. 14.13). However, when psoriasis presents on the moist skin of the vulva, the silver scaling typically seen elsewhere on the body is typically absent. Psoriasis affects only keratinized skin, with vulvar plaques commonly identified on the mons pubis.[29] Although psoriasis may be limited to the vulva, other areas of the body (scalp, extensor surfaces, and trunk) are usually affected. Psoriasis is associated with Köbner phenomenon (i.e., the disease can flare at any site of injury, including surgical sites). As with LS and erosive LP, loss of vulvar architecture may occur.

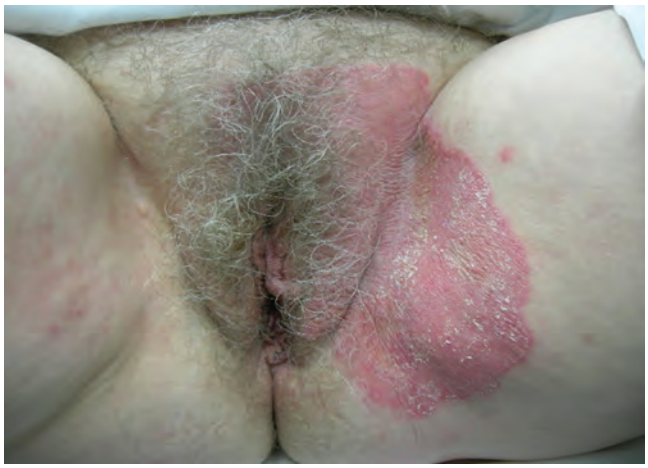

FIGURE 14.13 Psoriasis. (Typical clinical features: well-demarcated, symmetric "salmon pink" plaques, with silvery scale.) (From C. K. Stockdale personal library.)

The diagnosis of nonvulvar psoriasis is usually made based on history and physical examination. Occasionally, a skin biopsy using a 4-mm punch biopsy may be needed to rule out other conditions, but there are no other lab tests to confirm or exclude the diagnosis. In cases of vulvar psoriasis, the differential diagnosis includes tinea cruris, intertrigo, seborrheic dermatitis, and lichen simplex chronicus. Definitive diagnosis is made through biopsy, although in more long-standing cases, biopsy may be nonspecific and interpreted as psoriasiform dermatitis. A negative biopsy, then, does not preclude the presence of disease.[63,64]

When limited to the vulva, local treatment with low- to midpotency topical corticosteroids is the treatment of choice. Friction and occlusion may precipitate vulvar psoriasis flares. Thus, attention to vulvar hygiene measures is imperative for control of symptoms. If not adequately controlled, topical calcipotriene or calcitriol and the topical calcineurin inhibitors, tacrolimus or pimecrolimus, may be used as additional first-line therapies. For unresponsive disease, systemic therapy with oral methotrexate, retinoids, anthralin, cyclosporine, alefacept (Amevive), etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), ustekinumab, or ultraviolet (UV) light may be considered in consultation with a physician experienced with the use of such medications.[63]

TABLE 14.6 Indications for Specialist Referral for Patients With Lichen Sclerosus

- Symptoms are not controlled with potent topical corticosteroids applied three or more times weekly or after using >30 g over 6 months.
- Localized skin thickening/hyperkeratosis unresponsive to topical steroids
- Patients with prior treatment for usual or differentiated type VIN and/or SCC
- Vulvar biopsy is consistent with carcinoma or precancerous changes.
- Biopsies where the pathologist cannot make a definite diagnosis of differentiated VIN but there is suspicion for its presence

From Jones RW, Scurry J, Neill S, et al. Guidelines for the follow-up of women with vulvar lichen sclerosus in specialist clinics. *Am J Obstet Gynecol.* 2008;198(5):496.e1–496.e3.

Lichen Planus

LP, an inflammatory mucocutaneous disorder most likely related to cell-mediated immunity, exhibits a wide range

of morphologies. It tends to occur in the third to sixth decades of life. It may occur as a generalized skin eruption or it may be isolated to the vulva. Estimates suggest that less than 2% of women are affected by LP.[29] Up to 50% of women with LP elsewhere on their body have vulvar involvement as well, although vulvar involvement is often underreported and underdiagnosed.[65] The etiology of LP is not known but likely involves some form of autoimmune response and it is often associated with other autoimmune disease. Symptoms often include intense pruritus or vulvar pain, soreness, or burning. Symptoms may be constant or intermittent in nature (Fig. 14.14).

There are three types of LP that affect the vulva: erosive, papulosquamous, and hypertrophic. The most common form and the most difficult to treat is the erosive form, which often involves the vagina. Recurrences, slow healing, significant scarring, and pain are common. Dyspareunia and difficulty with urination or dysuria may result. Lesions of erosive LP appear as shiny, brightly erythematous erosions with white striae or a white border (Wickham striae) seen along the margins (Fig. 14.15). Erosive lesions may also present as white epithelium or as red or purple papules. Lesions may be isolated or they may be associated with marked architectural destruction of involved areas.

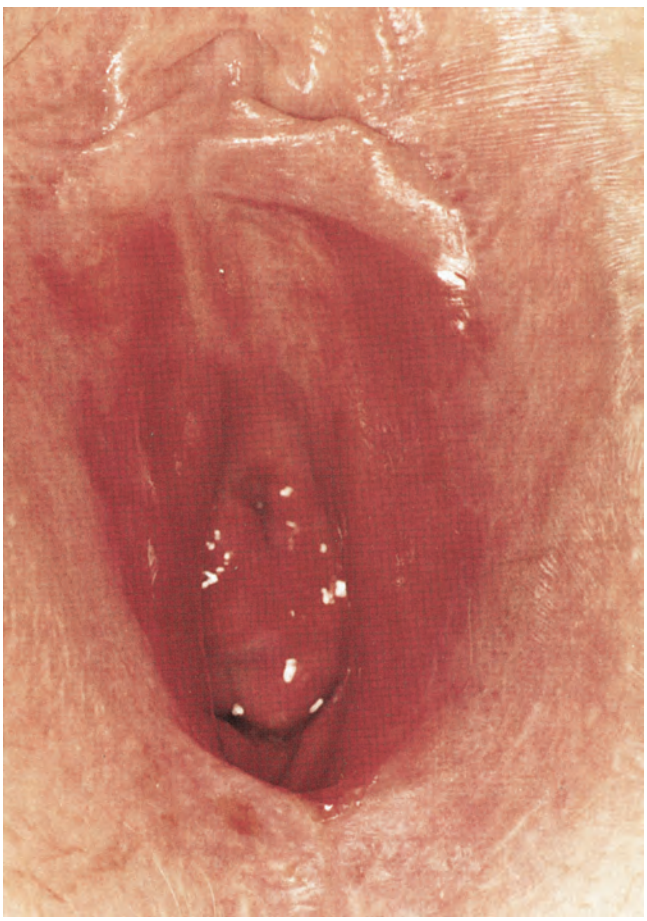

FIGURE 14.14 Lichen planus in a patient with dyspareunia for 8 months. Condition involved vagina and vestibule. Acute vaginal occlusion necessitated vaginal dilators (candlesticks) and topical steroids (Cort-Dome suppositories). (From Wilkinson EJ, Stone IK, eds. *Atlas of Vulvar Disease*. Philadelphia: Lippincott Williams & Wilkins; 2012:26.)

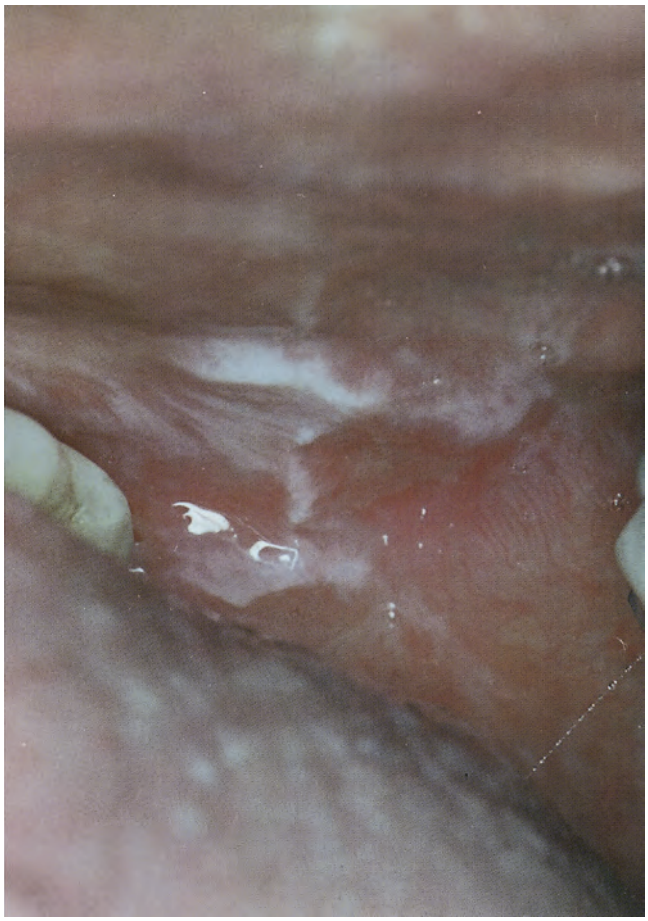

FIGURE 14.15 Reticular buccal mucosa lesion in a patient with vulvovaginal lichen planus. (From Wilkinson EJ, Stone IK, eds. *Atlas of Vulvar Disease*. Philadelphia: Lippincott Williams & Wilkins; 2012:27.)

Vaginal mucosal involvement may occur in up to 70% of women with vulvar erosive LP. The vaginal involvement may be limited to discrete areas of inflammation and discharge or there may be massive inflammation and denudation of the entire vagina. In very severe cases, vaginal adhesions and synechiae may result in narrowing or even obliteration of the vaginal canal.[66,67] Vaginal involvement may occur without vulvar involvement; cervical involvement may lead to atypia on Pap smears.

Symptoms commonly reported by patients with erosive vulvar LP include dyspareunia, burning, and increased vaginal discharge.[68] Examination of the vaginal discharge reveals predominance of inflammatory cells and immature parabasal and basal epithelial cells (these will appear small and round, with relatively large nuclei). The vaginal pH is increased, usually in the range of 5 to 6. This discharge has often been labeled as desquamative inflammatory vaginitis (DIV), but whether DIV is a type of erosive LP or a distinct type of vaginitis remains controversial.[66,67]

In a recent case series of women with vulvovaginal LP, 55% gave a personal and/or family history of an autoimmune disorder, including diabetes mellitus, thyroid disease, and celiac disease.[69] Setterfield et al.[69] also found that the human leukocyte antigen DQB1*0201 allele was present in 80% of women with vulvovaginal LP, suggesting a genetic predisposition to the vulvovaginal form of LP. Nevertheless, these associations have not been consistently identified in diverse populations. An association between LP and SCC has been identified, thus women with LP should be followed carefully. The actual risk of malignancy has been difficult to determine given the rarity of both disorders.[68]

The vulvovaginal-gingival (VVG) syndrome is a variant of erosive LP that involves the epithelium of the vulva, vestibule, vagina, and mouth. Lesions in these areas may or may not be concurrent. This form of erosive LP is exceptionally difficult to treat.

The diagnosis of LP is based primarily on characteristic clinical signs and symptoms, although a biopsy may be obtained to support the clinical diagnosis. The shave or punch biopsy should be taken from the most developed lesion. If a biopsy is done of an ulcerated area, it is important to include a small rim of normal epithelium along with the affected tissues. Tissue biopsies in cases of erosive LP are often diagnostic.

The differential diagnosis of LP includes other inflammatory dermatoses. On occasion, the skin may appear uniformly white, and LP is commonly confused with LS. However, vaginal involvement is common in erosive LP and is rare in LS. Like psoriasis and LS, LP can exhibit Köbner phenomenon (i.e., the disease can flare at any site of injury, including surgical sites). Biopsy may be helpful and can help rule out immunobullous diseases, such as cicatricial pemphigoid, bullous pemphigoid, and pemphigus vulgaris, which may mimic LP.[70]

The prognosis for spontaneous remission of vulvovaginal LP is poor. Treatment, although not curative, can improve patients' symptoms and sense of well-being. There is no single effective treatment for erosive LP, and it is often resistant to therapy. In comparison, papulosquamous and hypertrophic forms of vulvar LP usually respond to treatment. Ultrapotent topical glucocorticoids such as clobetasol or halobetasol propionate 0.05% are first-line therapy, with the ointment being used for external vulvar lesions nightly (or twice a day if the disease is severe) for 1 to 2 months followed by re-evaluation. Corticosteroid suppositories or foams may be used intravaginally if necessary. If there is a response, the glucocorticoid use may be decreased to one to three times per week for 12 weeks. Because the symptoms may recur after the therapy is stopped, a maintenance therapy with a midpotency or low-potency glucocorticoid ointment may be used one to three times weekly indefinitely. Patients should be told that only a 2- to 3-mm size dot of ointment is necessary and they should be shown, using a mirror, exactly where to place the ointment.

Corticosteroid suppositories or foams may be used intravaginally if necessary. Suggested regimens include 25 mg suppositories of hydrocortisone intravaginally twice a day for 2 months or 50 mg every day for mild and early disease.[71] In severe cases, doses up to 100 mg may need to be used (and may require compounding to obtain) every night for 2 weeks and then every other night for an additional 2 weeks. If no improvement is seen, the regimen of 100 mg every night may need to be extended for up to 3 months and then converted to maintenance treatments (two to three times weekly) that are determined by the level of decline in inflammation seen on microscopy. If there is still no response, referral to a specialist in vulvar dermatoses should be strongly considered.

When used intravaginally, care should be taken to monitor the potential side effects of high-dose steroids, including not only atrophy, striae, and steroid dermatitis but also systemic absorption resulting in adrenal suppression. With frequent use of steroids, infections (e.g., yeast, herpes) should also be suspected when symptoms flare.[66] To help maintain vaginal patency, the use of vaginal dilators should be encouraged. Surgery in general is not advocated. Despite treatment, significant control of symptoms and restoration of sexual function is difficult in women with genital erosive LP.

If the vulvar disease is too severe to allow for topical application of glucocorticoids, a single IM dose of triamcinolone (1 mg/kg) maybe given followed by topical therapy 2 to 3 weeks later. It may be helpful to apply petrolatum jelly to the vulva during the interval between IM injection and topical application of glucocorticoids to help minimize further erosion.

Therapeutic options, shown in small trials to be effective, include topical and systemic corticosteroids, topical and oral cyclosporine, topical tacrolimus, hydroxychloroquine, oral retinoids, methotrexate, azathioprine, and cyclophosphamide.[70]

If a synchronous bacterial or fungal infection is suspected, these should be treated appropriately, whereas use of the glucocorticoid therapy is continued.

Plasma Cell Vulvitis

Plasma cell vulvitis, also termed Zoon vulvitis or vulvitis circumscripta plasmacellularis, is a rare, benign, chronic inflammatory mucositis of unclear etiology (Fig. 14.16). It is described most often in postmenopausal women presenting with intractable vulvar pruritus, burning, dyspareunia, and dysuria. It has been postulated to be an autoimmune disease with exacerbation stemming from constant rubbing and chronic infection. Physical findings include atrophic, glistening, and erythematous patches.[72] Lesions are most often seen on the medial surface of the labia minora and periurethral mucosa and near the vestibule of the vagina. The diagnosis is confirmed by histology, characterized by dermal infiltration with plasma cells. Despite the hallmark histopathology findings, misdiagnosis is common.[73] The

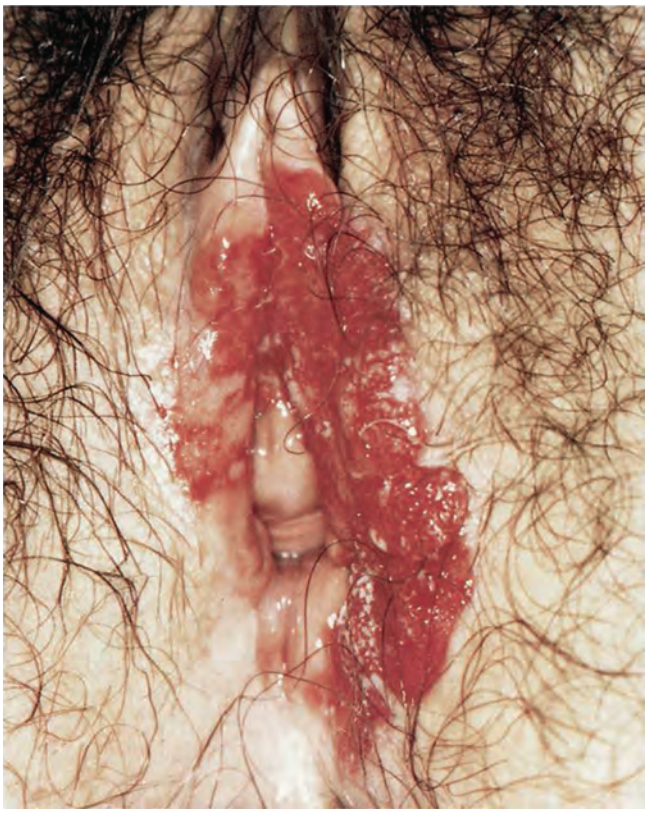

FIGURE 14.16 Plasma cell vulvitis. A red, erosive-appearing lesion occupies the vulvar vestibule, medial aspects of the labia minora, and a portion of the perineal body. (Courtesy of Dr. Frits B. Lammes, Amsterdam, The Netherlands.)

differential diagnosis includes Paget disease, pemphigus/pemphigoid, LP, fixed drug eruption, and cancer. Response to treatment has been inconsistent with flares and remissions. As with many vulvar dermatoses, the first-line treatment is topical corticosteroids. In women with resistant disease, other treatments have been described including intralesional steroids, topical tacrolimus, topical misoprostol, imiquimod, etretinate, and surgery.[74,75]

BENIGN PIGMENTED LESIONS

Benign pigmented lesions are somewhat common findings on the vulva (Table 14.7). Nonetheless, diagnosis is essential to exclude malignancy or VIN given their variable appearance. Although vulvar melanoma is exceedingly rare, it is the second most common invasive cancer occurring in the vulva. Thus, any pigmented vulvar lesion that is 5 mm or larger, friable, or is noted to have recent changes in size, shape, and color mandates a biopsy.

VULVOVAGINAL CYSTS

Vulvar and vaginal wall cysts are common, and in most cases, an accurate diagnosis can be made on history and physical examination. During physical examination, the lesion should be assessed for location, mobility, tenderness, definition, and consistency. Malignancy must always be considered in the differential diagnosis.

Bartholin Cysts

The Bartholin glands, also referred to as the greater vestibular glands, are located at the 4 and 8 o'clock positions at the vaginal orifice and are normally not palpable. Bartholin duct cyst is the most common cystic growth in the vulva, occurring primarily in younger reproductive age women. The majority of these are unilateral nontender cystic masses in the lateral introitus transected by the labia minora. Ductal obstruction due to infection or thickened mucus leads to cyst formation.[76]

TABLE 14.7 Common Benign Pigmented Vulvar Lesions

	Appearance	Treatment
Nevi	Common pigmented lesion consists of nevus cells. They have a wide variety of appearances and may range in size from a few millimeters up to 2 cm.	Biopsy if 5 mm or larger of if appears suspicious
Melanosis	Flat, pigmented area; termed lentigo simplex if <5 mm in diameter and melanosis if larger	Not indicated beyond biopsy for diagnosis
Cherry hemangioma	Painless, cherry red to black papules that may occur anywhere on the skin and contain an abnormal proliferation of blood vessels; when present on the vulva, they may be confused for melanoma.	Easily confirmed by noting blanching when compressed
Seborrheic keratosis	Multiple, macular or papular pigmented lesions with a waxy consistency to palpation	Biopsy to exclude VIN; may consider excision, cryotherapy, or topical imiquimod
Acanthosis nigricans	Pigmented, raised, papillomatous lesion	Not indicated beyond biopsy for diagnosis
Vitiligo	White, nonpigmented area (results from a loss of melanin)	Not indicated (beyond cosmetic)
Intertrigo	Erythematous, macerated area typically seen in moist flexural areas (beneath an abdominal pannus or along the genitocrural folds).	Keep involved area clean and dry; consider evaluation for an associated fungal or bacterial infection and treat if present.

Data from Wilkinson EJ, Stone KI. *Atlas of Vulvar Disease*. Baltimore: Lippincott Williams & Wilkins; 1995; Ference JD, Last AR. Choosing topical corticosteroids. *Am Fam Physician*. 2009;79(2):135–140.

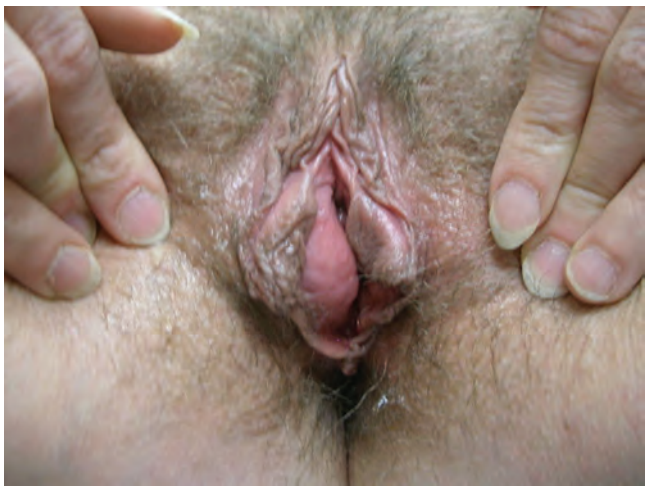

FIGURE 14.17 Bartholin duct cyst. (Classic presentation, cystic mass in the lateral introitus transected by the labia minora.) (From C. K. Stockdale personal library.)

The diagnosis of Bartholin cysts and abscesses is clinical and readily made on visual vulvar examination. Most are 1- to 3-cm large, and they are often asymptomatic (unless they are large enough to cause dyspareunia or discomfort with walking or sitting). The classic, medially protruding cystic structure at the inferior aspect of the labia (4 and 8 o'clock position) crossed by the labium minus is almost certainly a Bartholin cyst (Fig. 14.17). The differential diagnosis of Bartholin cysts includes all vulvar masses (e.g., vulvar lipoma, fibroma). Other cysts that should be considered in the differential diagnosis are identified in Table 14.8. The occurrence of fistula should be considered in women presenting with persistent purulent drainage and granulation tissue involving Bartholin duct. Bartholin gland carcinoma, although exceedingly rare (incidence less than 1 in 500,000 women), should be considered in the postmenopausal woman.[77]

Treatment of Bartholin cyst can be conservative or surgical depending on the patient's age, symptoms, the size of the cyst, and whether it is recurrent or infected.[78–80] Current treatment modalities include outpatient procedures such as needle aspiration with antibiotic coverage (if indicated for Bartholin abscess), incision and drainage with/without placement of a Word catheter, as well as more extensive surgical therapies (such as duct marsupialization or gland excision). The overall success rate (marked by the absence of swelling, discomfort, and appearance of a freely draining duct) is 85% regardless of the treatment method employed.[80]

Incision and drainage is a simple procedure, which is quick and easy to perform and gives immediate relief to the patient. However, it is generally not advocated because of a high rate of recurrence and increased difficulty with subsequent Word catheter placement or marsupialization due to scarring.[81]

In contrast, Word catheter placement following incision allows for formation of an epithelialized tract and continued drainage of the gland, thereby reducing recurrences. Although the Word catheter is a safe, simple, and effective outpatient treatment for a Bartholin abscess, it is typically considered as an alternative to

TABLE 14.8 Vulvar Cysts to Consider in the Differential Diagnosis of Bartholin Cysts

	Appearance	Treatment
Mucous cyst of the vestibule	Mucous cysts occur primarily in the vulvar vestibule and arise from occlusion of minor vestibular ducts and tend to be soft, <2 cm in diameter, superficial, and smooth.	Treatment is not indicated in the absence of symptoms.
Cyst of the canal of Nuck	Cystic swelling in the inguinal crease or anterior labia majora. These cysts arise from remnants of peritoneum that accompanies the round ligament into the labium majus through the inguinal canal. Cysts may occur anywhere along the path of the inguinal canal or within the labia majora. Associated with an inguinal hernia in up to one-third of patients.	Treatment must include ligation of the peritoneal sac at the inguinal ligament. The cyst will reoccur if simple aspiration is attempted.
Epidermal inclusion cyst (also called sebaceous, keratinous, or epidermoid cysts)	Cysts tend to be asymptomatic, small (2–5 mm), multiple, and grouped occurring on the labia majora. Cysts are filled with keratinous material that is white to pale yellow in color and cheesy in character.	Treatment by excision is not necessary unless the cyst is symptomatic (pain or recurrent infection) or the diagnosis is in question.
Vulvar hematoma	Usually the result of trauma or intraoperative bleeding. Extravasated blood my expand the loose areolar tissue of the labia and cause considerable swelling. This tense swelling is exquisitely painful.	Observation and packing (if possible) may reduce extent of hematoma. Incision, drainage, and ligation of bleeding vessels should be undertaken for enlarging hematomas.
Adenocarcinoma of the Bartholin gland	The classic presentation of Bartholin gland cancer is an irregular, nodular mass in the region of the Bartholin duct and gland. This rare malignancy should be considered in menopausal women with an irregular Bartholin mass.	Biopsy or excision for diagnosis.

Data from Wilkinson EJ, Stone KI. *Atlas of Vulvar Disease*. Baltimore: Lippincott Williams & Wilkins; 1995; Edwards L, Lynch PJ. *Genital Dermatology Atlas*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

marsupialization.[82] A small incision is made proximal to the hymenal ring, the catheter is inserted and inflated, and the catheter end tucked into the vagina. Removal should not occur until a fistulous tract forms (4 to 6 weeks). Complications of the Word catheter include pain during and after placement and difficulty maintaining the catheter in the correct place.[78,83]

Marsupialization is often employed following failure of the less invasive therapies and has traditionally been the "gold standard" of treatment. Conventional marsupialization consists of incision of the cyst or abscess and suturing of the edges of the cavity to the skin (just distal to the hymenal ring within the introitus into the region of the normal duct). The procedure has been modified by excising a 2- to 3-cm oval portion of the vestibular skin overlying the cyst or abscess and a smaller oval portion of the cyst wall prior to suturing of the edges to improve patency of the opening during the healing process and thus reduce the likelihood of subsequent recurrence. In many cases, marsupialization may be done in the office with either local anesthesia or a pudendal block. Complications of marsupialization include pain, hematoma formation, prolonged healing, and dyspareunia due to scarring.[83,84]

The management of Bartholin abscesses should include routine culture for anaerobic and aerobic bacteria as well as testing for *Neisseria gonorrhea* and *Chlamydia trachomatis*. Bartholin duct cysts are usually sterile, and the gland is not affected. However, when infection is present, it is often polymicrobial. Broad-spectrum antibiotic coverage is indicated when cellulitis is present and should be tailored to the culture results. Additionally, diabetic patients or others at risk for complicated infection warrant close observation due to their susceptibility to necrotizing infection, and this may include inpatient management. One suggested treatment regimen for these patients is cefixime (400 mg orally daily for 1 week) and clindamycin (300 mg orally four times a day for 1 week). Excision of the entire Bartholin gland and duct is reserved for recurrent abscess/cyst formation given risk for significant morbidity including hemorrhage, hematoma formation, infection, damage to the rectum, and dyspareunia.[81]

Primary carcinoma of the Bartholin gland is rare (less than 5% of all vulvar cancers) and is usually an adenocarcinoma. Prevalence is highest in women in their 60s, and it often presents as a painless vulvar mass. It is generally recommended that women older than the age of 40 years with either a Bartholin gland cyst or abscess undergo biopsy of the Bartholin gland to rule out carcinoma. Excision is associated with more morbidity than biopsy and, as noted previously, the incidence of cancer of the Bartholin gland is extremely rare.

Skene Duct Cysts

Skene (paraurethral) cysts are rare and result from ductal occlusion (Fig. 14.18). The diagnosis is based on location (typically suburethral). However, Skene duct cyst must be distinguished from a urethral diverticulum. Although compression of a urethral diverticulum may result in urethral urine extravasation, compression of a Skene duct cyst will not. Imaging with magnetic resonance imaging (MRI) may be useful to further distinguish a Skene cyst from a urethral diverticulum. Ultrasound may also be used to try to differentiate between a urethral diverticulum and Skene duct cyst. Treatment beyond observation is not required for small, asymptomatic Skene cysts. Excision is required for Skene cysts that are painful or interfere with urination.

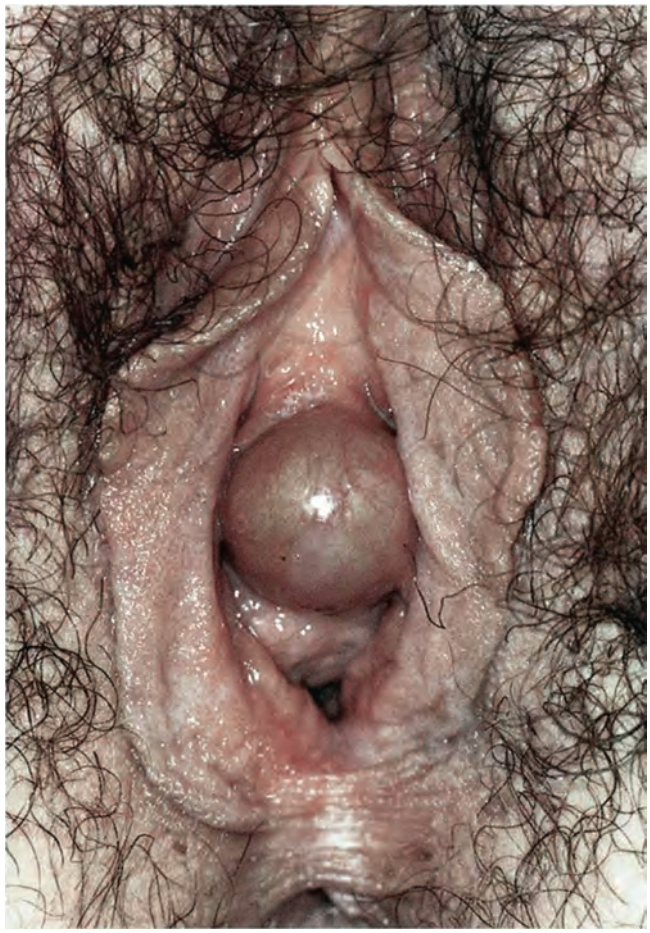

FIGURE 14.18 Skene duct cyst (periurethral cyst). (From Wilkinson EJ, Stone IK, eds. *Atlas of Vulvar Disease*. Philadelphia: Lippincott Williams & Wilkins; 2012:20.)

Müllerian Cysts

The most common vaginal cysts arise from Müllerian embryologic remnants. They typically vary in size from 1 to 7 cm and may occur anywhere in the vaginal wall, although they are most commonly found in the anterolateral wall. Small asymptomatic cysts may be noted on routine annual examination and do not require treatment. Excision or marsupialization may be performed for large symptomatic cysts.

Gartner Duct Cysts

Gartner duct cysts arise from Wolffian remnants and occur on the lateral vaginal sidewalls. They are usually 1 to 2 cm in diameter and are firm on palpation. Distinction between a Müllerian cyst and Gartner duct cyst is not clinically relevant. As with Müllerian cysts, excision may be considered for large or symptomatic cysts. In rare cases, a Gartner duct cyst may communicate with an ectopic ureter. For this reason, patients with known congenital urinary tract abnormalities and a vaginal wall mass, imaging may be indicated.

SOLID TUMORS

Patients may present for concern of "a lump" after discovering a growth on the vulva (Table 14.9). The anxiety level in this situation is usually high because the patient presumes it is malignant. Fortunately, most of these growths are benign. The clinician, however, must be aware of the potential for malignancy. Usually, biopsy or complete removal of any growth is required. This can be performed in an elective fashion in the office or operating room, depending on the size and location of the lesion.

SYSTEMIC CONDITIONS ASSOCIATED WITH VULVAR OR VAGINAL MANIFESTATIONS

Systemic disorders including autoimmune diseases and connective tissue disorders may present with varied and broad-ranging skin manifestations. Rarely, such manifestations are the initial presenting symptom, especially when limited to vulvar or vaginal findings.

Crohn Disease

Crohn disease is a chronic granulomatous disorder affecting the gastrointestinal tract. Metastatic Crohn disease is defined as distant skin involvement of the same granulomatous inflammatory changes and is less well recognized owing to its variable presentation and rare occurrence.[85] Typically, gastrointestinal involvement precedes skin involvement. However, cutaneous manifestations may be present without a documented history of gastrointestinal disease. In some cases, vulvar manifestations of Crohn disease may appear several years before active intestinal disease becomes manifest. Any spontaneously developing fistulae, recurrent fistulae, or recurrent perineal abscesses should raise suspicion for Crohn disease.

About 33% of women with Crohn disease have gynecologic complications. The classic appearance of vulvar Crohn disease is described as "knife-like" ulcerations occurring in skin creases (Fig. 14.19). Lesions may be contiguous with rectal involvement or may be metastatic disease from the bowel. Other vulvar and perianal manifestations include persistent inflammation, nonhealing ulcers, and fistulae formation. Diagnostic confirmation of enterovaginal fistulas may be difficult; techniques for diagnosis include methylene blue enemas (after insertion of a tampon in the vagina), a radiologic study using a water-soluble contrast during a rectal enema, or a fistulogram. Fistula repair in Crohn disease is associated with a very high failure rate.

TABLE 14.9 Benign Solid Tumors of the Vulva

	Appearance	Treatment
Fibroma	Most common benign, solid vulvar tumor; arises from fibrous tissue; firm, asymptomatic lesion typically occurring on the labia majora, perineal body, or introitus; tends to be pedunculated and ranges in size	Excision to exclude malignancy
Lipoma	Second most common solid vulvar tumor; skin colored, soft, fatty tumor of the subcutaneous tissue; typically asymptomatic and slow growing.	Excision if symptomatic or enlarging
Acrochordon	Fibroepithelial polyps or "skin tags" are also commonly noted on the vulva.	Excision if symptomatic or enlarging
Mammary tissue	May occur along the "milk line" from the breast down to the vulva; typically unnoticed until the patient is pregnant or lactating	Excision
Endometriosis	Uncommon solid, cystic, or mixed bluish, brown, or black lesion; usually secondary presentation of pelvic endometriosis occurring in a scar (i.e., episiotomy or vaginal cuff following hysterectomy); the patient may note cyclical, painful swelling.	Systemic therapy, excision, or destruction (electrocautery or laser)
Hidradenoma	Uncommon solitary, nontender lesions typically located in the interlabial sulcus	Excision for diagnosis or if symptomatic
Fox-Fordyce disease	Uncommon pruritic, small, firm, flesh-colored, or hyperpigmented papules occurring on the mons, labia majora, and axillae	Local corticosteroids and comfort measures to reduce symptoms; rarely, excision.
Syringomata	Small, firm, skin-colored to brown papules; most commonly occur on the eyelids (diagnosis is confirmed if present elsewhere)	Reassurance

Data from Wilkinson EJ, Stone KI. *Atlas of Vulvar Disease*. Baltimore: Lippincott Williams & Wilkins; 1995; Edwards L, Lynch PJ. *Genital Dermatology Atlas*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

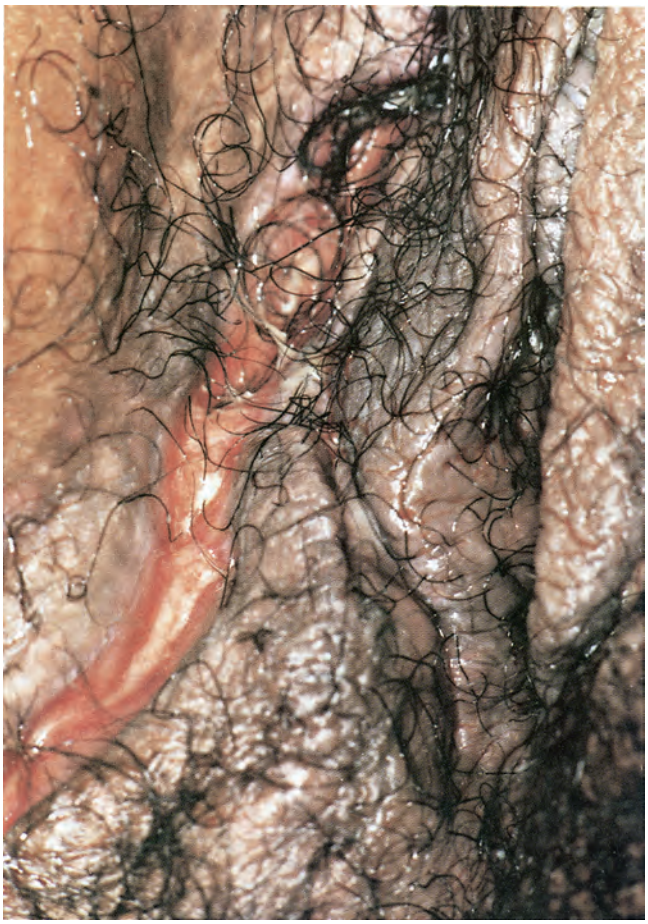

FIGURE 14.19 Deep vulvar ulceration in a patient with Crohn disease of the vulva and bowel for approximately 9 years. Exacerbation of vulvar disease was unresponsive to prednisone 60 mg orally every day and metronidazole 500 mg orally three times a day. Imuran was started at 100 mg orally every day. (From Wilkinson EJ, Stone IK, eds. *Atlas of Vulvar Disease*. Philadelphia: Lippincott Williams & Wilkins; 2012:152.)

Metastatic Crohn disease is recalcitrant to treatment and is best managed with systemic steroids or other systemic immunosuppressive agents in consultation with gastrointestinal specialists. Rarely, vulvectomy may be considered in cases refractory to medical therapy.

Behçet Syndrome

Behçet disease is a rare condition found predominantly in the Mediterranean, the Middle East, and Japan, with a prevalence of approximately 1 in 300,000. This multisystem disorder classically affects the oral mucosa, skin, joints, gastrointestinal tract, and central nervous system (including eyes). Most of the clinical manifestations result from vasculitis. In areas where it is common, men and women are affected equally, although in the United States and Northern Europe, it is more common in females. It typically affects patients between 20 and 40 years of age. Pathology is nonspecific.

Clinically, Behçet disease presents with recurrent, usually painful mucocutaneous ulcers (commonly referred to as canker sores) (Fig. 14.20). The outer portions of the lips are not involved. Severity seems to be greater in men. Up to two-thirds of patients may have ocular involvement and up to one-third have vascular manifestations. Behçet disease is unusual in that it may involve arterial or venous vasculature anywhere and of any size.

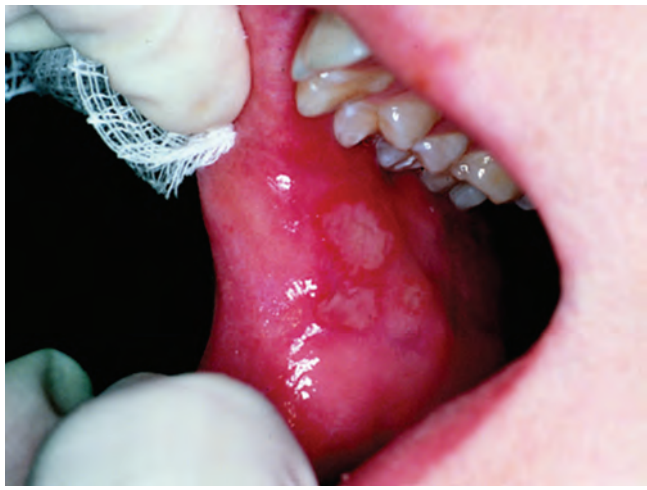

FIGURE 14.20 Behçet disease. (From Neville BW, Damm DD, White DK. *Color Atlas of Clinical Oral Pathology*. 2nd ed. Baltimore: Lippincott Williams & Wilkins; 1998.)

The diagnosis is based on clinical criteria defined by the International Study Group and includes recurrent oral ulcerations (more than three times in 1 year) plus two of the following: recurrent genital ulceration, eye lesions, skin lesions, or positive pathergy test.[86] The differential diagnosis for Behçet disease is extensive and more common causes of vulvar ulcers and erosions should be ruled out, e.g., HIV, syphilis, chancroid, Crohn disease, and lupus, to name a few.

Genital ulcerations occur in at least 75% of patients with Behçet disease. The lesions are similar in appearance to the oral ones and are usually painful. Genital ulcerations do not recur as frequently as oral ones, but scar formation is more common.

When oral and genital ulcers are present, but the criteria for Behçet disease are not met, the diagnosis is oral–genital aphthosis.

As with other waxing and remitting systemic disorders, an ideal therapeutic regimen does not exist. Patients with Behçet disease are typically managed in consultation with a rheumatologist.

Neurofibromatosis

Neurofibromatosis type 1 (Von Recklinghausen disease) is an autosomal dominant progressive disorder with an incidence of approximately 1 in 3000 births.[87] The classic cutaneous findings include café au lait spots and neurofibromas. Genital involvement is extremely unusual and is limited to sporadic case reports. Excision is

required for diagnosis as well as treatment of symptomatic tumors.

Cicatricial Pemphigoid

Vulvar presentation of pemphigoid is uncommon, and when present, is more likely cicatricial pemphigoid (also termed mucous membrane pemphigoid) rather than bullous pemphigoid. Cicatricial pemphigoid is an autoimmune disease that results in blistering of the mucosal surfaces and occurs mostly in older patients. Patients may present with superficial vulvovaginal ulcers, desquamative vaginitis, and conjunctivitis. Mucosal erosion with subsequent scarring may result in labial fusion and vaginal stenosis. Diagnosis is made by biopsy of a lesion. This progressive scarring disease should be aggressively treated in consultation with a dermatologist.

Graft Versus Host Disease

Graft versus host disease (GVHD) is a multisystem disorder that occurs in the setting of an allogenic bone marrow transplant. Donated T lymphocytes proliferate and attack host cells. Vulvovaginal findings include an erosive vulvovaginitis clinically indistinguishable from erosive LP. Treatment is similar to that for erosive LP.

VULVOVAGINAL ATROPHY

Estrogen deficiency leads to thinning of the vaginal and vestibular epithelium. Most commonly encountered in postmenopausal women, conditions with relative estrogen deficiency, such as the postpartum period with breast-feeding or oral contraceptive use may also result in symptomatic atrophic changes (Table 14.10).

Estimates suggest that up to 40% of postmenopausal women experience symptoms from atrophic changes.[88] Perimenopausal women who do not have visible signs of vulvovaginal atrophy can also experience symptoms of vulvar irritation and dryness.[89] Additionally, up to 25% of estrogen replacement users will continue to experience symptoms of urogenital atrophy despite improvement in other symptoms associated with estrogen deficiency.[90]

TABLE 14.10 Vulvar Vaginal Physical Changes Associated With Loss of Estrogen

Vulvar manifestations:
Hypopigmented, smooth, nonelastic, thin, or shiny skin
Loss of collagen, adipose, and water-retaining ability of the skin
Petechiae and/or microfissures
Atrophy of the clitoral prepuce
Labial fusion
Sparse pubic hair
Vaginal manifestations:
Changes in the quantity and quality of vaginal secretions (dryness)
Loss of elasticity, rugation, and thinning of the vaginal mucosa
Shortening and narrowing of the vaginal canal
Coaptation of the vaginal vault from ulceration and denudation of friable thin mucosa

Data from Wilkinson EJ, Stone KI. *Atlas of Vulvar Disease*. Baltimore: Lippincott Williams & Wilkins; 1995; Edwards L, Lynch PJ. *Genital Dermatology Atlas*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

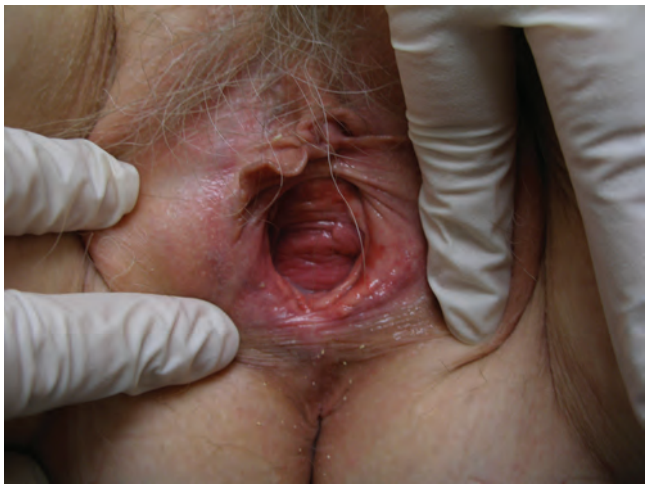

FIGURE 14.21 Atrophy. (The vestibule is pale and thin with superficial excoriations.) (From C. K. Stockdale personal library.)

As women approach menopause, vulvar tissue becomes increasingly sensitive to irritants,[64] and in the absence of estrogen, the vulvovaginal area becomes pale, thin, and often dry (see Table 14.7). Some common vulvar/vaginal physical changes associated with loss of estrogen are seen in Figure 14.21. Activities that once were not associated with discomfort may become so. Vaginal secretions are reduced, the vaginal pH becomes more alkaline, and the vaginal flora is altered.[91,92] The genital area becomes increasingly susceptible to trauma, chemical irritants, and bacterial overgrowth. In severe atrophic vaginitis, a purulent, noninfectious discharge may develop along with fissuring of the vestibule. The diagnosis is made based on an elevated vaginal pH (range of 6.0 to 7.5) and the presence of parabasal or intermediate cells on microscopy.[3]

Management options include lifestyle modification strategies, the use of vaginal moisturizers, and low-dose vaginal estradiol preparations. Maintaining regular vaginal intercourse provides protection from urogenital atrophy by increasing blood flow to the pelvic organs.[93] The use of a nonhormonal vaginal moisturizer, such as Replens, has been shown to exert a beneficial effect similar to that of local hormone replacement,[94,95] although the same cannot be said of vaginal lubricants.[89] Treatment of vaginal atrophy can also be accomplished through a variety of locally applied estrogenic preparations.

In a systematic review of local estrogen for the treatment of vaginal atrophy in postmenopausal women, efficacy was found to be significantly improved with the use of the cream, ring, and tablets when compared to placebo and nonhormonal gels. Side effects associated with all forms of topical estrogen therapy include the possibility of endometrial hyperplasia. Yearly progestogen challenge or endometrial evaluation (direct sampling or ultrasound)

may be considered. However, the risks of long-term topical estrogen therapy in asymptomatic women (e.g., no vaginal bleeding) remain unclear. Lastly, systemic estrogen therapy, although efficacious, raises concerns for many women and may not be sufficient to relieve the symptoms of urogenital atrophy.[96]

VULVODYNIA

Vulvodynia, an underrecognized and poorly treated multifaceted dysfunction, significantly interferes with intimacy, relationships, and overall quality of life for affected women and their partners. Limited studies have focused on etiology, treatment, and outcome regarding vulvar pain disorders. Thus, management is often based on "trial and error" and is typically frustrating for practitioners, patients, and significant others owing to the complex interrelated medical, psychological, and psychosexual components.

Vulvodynia has been defined as a vulvar discomfort, most commonly described as burning pain, occurring in the absence of relevant visible findings (such as infection or inflammation) or a specific, clinically identifiable neurologic disorder (e.g., postherpetic neuralgia).[97,98] Current evidence indicates that the lifetime cumulative incidence of vulvodynia approaches 15%, which suggests that nearly 14 million American women will at some point in their lives experience the symptoms of chronic vulvar burning and pain.[99] Indeed, a localized form of vulvodynia involving the vulvar vestibule is thought to be the leading cause of painful intercourse in premenopausal women.[100,101]

Patients with vulvodynia tend to fall into different groups based on the location of their pain. Generalized vulvodynia is used to describe involvement of the entire vulva by persistent, chronic pain that is burning, stinging, or irritating in nature, whereas localized vulvodynia specifies involvement of only a portion of the vulva, most commonly the vestibule (termed vestibulodynia or vulvar vestibulitis). In both generalized and localized vulvodynia, the pain may be provoked (i.e., triggered by physical contact of a sexual or nonsexual nature), unprovoked, or both. In the case of provoked pain, common triggers include, for example, vaginal intercourse, tampon insertion, and the wearing of tight-fitting clothing.[97]

Proposed precipitating factors for vulvar pain syndromes are numerous and have historically included histories of recurrent vaginal infections (most commonly candidal infections and bacterial vaginosis), use of oral contraceptives (particular early use), and destructive treatments (e.g., exposure to irritant agents such as trichloroacetic acid).

Women with vulvodynia have been found to have a higher incidence of irritable bowel syndrome and interstitial cystitis, which may be indicative of aberrant neuronal interactions (i.e., irritation of one organ leads to cosensitization of another). Other associated findings have included abuse and mood disorders. Harlow demonstrated an increased occurrence of childhood physical and sexual abuse in women with vulvodynia, an association largely confined to those harmed by a primary family member.[102] Both depression and anxiety are common with vulvar pain syndromes. However, whether depression, anxiety, and sexual dysfunction are causally related to, or are the result of, chronic vulvar pain syndromes remains unclear.[97] Although a multifactorial process is most likely involved in the development of vulvar pain (e.g., recurrent vaginal infections, use of oral contraceptives, history of destructive vulvar treatments), the end result appears to be neuropathically mediated pain manifested predominantly as burning.

An additional consideration in the assessment of patients with vulvar vestibulitis is the concomitant role of pelvic floor pathology. The pelvic floor changes seen in women with vestibulitis appear to be reactive in nature, a conditioned, protective guarding response which results from repeated attempts at vaginal penetration.[103] As a result of guarding and increased resting tone, any pressure applied to the vestibule leads to escalated pain, and the cycle becomes self-perpetuating. The pelvic floor hypertonicity seen in women with vestibulitis, then, appears to both maintain and exacerbate pain.

In evaluating vulvar pain or discomfort, the provider should ask the patient to characterize the pain as specifically as possible. They should also define the qualities of the pain the patient is experiencing as well as the duration and nature of the discomfort (i.e., generalized or localized, unprovoked or provoked, and either with or without spontaneous pain). Physical examination should be done with the possibility of other causes of vulvar discomfort in mind, such as ulcerations or lesions, and if these are noted, they should be biopsied or cultured as indicated. Other causes of vulvar pain may include pudendal neuralgia, diabetic neuropathy, and postherpetic neuralgia following herpes zoster infection (not herpes simplex). Multiple sclerosis may also produce pain syndromes. The vaginal examination should exclude other common causes of vulvovaginal irritation such as yeast or bacterial vaginosis.

In the absence of abnormal visible findings, the provider then performs the cotton swab test, an examination used to specifically localize any painful areas. A cotton swab is moistened, and then, starting at the thigh and moving medially toward the vaginal vestibule, the vulva is touched with the swab. The vestibule is systematically palpated with light pressure, and the patient is asked to rate the pain on palpation from 0 to 10 (10 is most painful), or a visual analogue pain scale is used. If pain is confirmed, a vaginal fungal culture is obtained in order to definitively rule out a yeast infection because yeast infections caused by atypical *Candida* species are often not obvious on examination. A negative fungal culture, in conjunction with the patient's history and positive findings on the cotton swab test, confirms

the diagnosis of vulvodynia.[104] A diagnostic algorithm proposed by Haefner et al.[104] is particularly useful in approaching the patient presenting with chronic (defined as three or more months) vulvar pain (Fig. 14.22).

Treatment recommendations, although numerous, rarely have been evidence-based. Although case series demonstrate improvement of symptoms with various treatment modalities including topical therapies (topical nitroglycerin, topical lidocaine, topical gabapentin cream, topical capsaicin), injectable therapies (interferon, steroids, botulinum toxin type A), systemic therapies, behavioral therapy, and surgery, further evaluation with randomized controlled trials often leads to disappointing results. Several placebo controlled studies have demonstrated a greater response in the placebo group (over therapy).[105] This clearly demonstrates the need for more rigorous prospective investigations with a placebo control when evaluating potential treatment response.

Thus, the current treatment options for vulvar pain are largely empirical. Tricyclic antidepressants (TCAs), the most studied of which is amitriptyline, and gabapentin have become mainstays of therapy for women with both generalized and localized vulvodynia.[106] Their use is largely based on evidence of efficacy from studies of other pain syndromes, including postherpetic neuralgia and diabetic neuropathy. Amitriptyline (10 to 75 mg) is typically started at 5 mg (half of a 10-mg tablet) and gradually increased so possible side effects are minimized. The dose is titrated up to 150 mg or symptom control, whichever comes first. Desipramine is also used and is less sedating; the dose schedule is the same as that of amitriptyline. For women who cannot tolerate TCAs, gabapentin may be considered. This is an anticonvulsant and is less sedating than the TCA therapies. It is started at a dose of 300 mg three times a day and may be increased up to a maximum dose of 1200 mg three times a day.[107] It should not be discontinued abruptly because it can lead to withdrawal-related side effects. Data confirming the efficacy of these medications in women with vulvar pain remains sparse. Although evidence from a large cohort study demonstrated pain improvement using amitriptyline in over 270 women with vulvodynia,[108] a subsequent randomized trial demonstrated amitriptyline with and without a topical steroid was not effective in treating vulvodynia.[109] A table of oral medications used to treat vulvodynia are listed in Table 14.11.

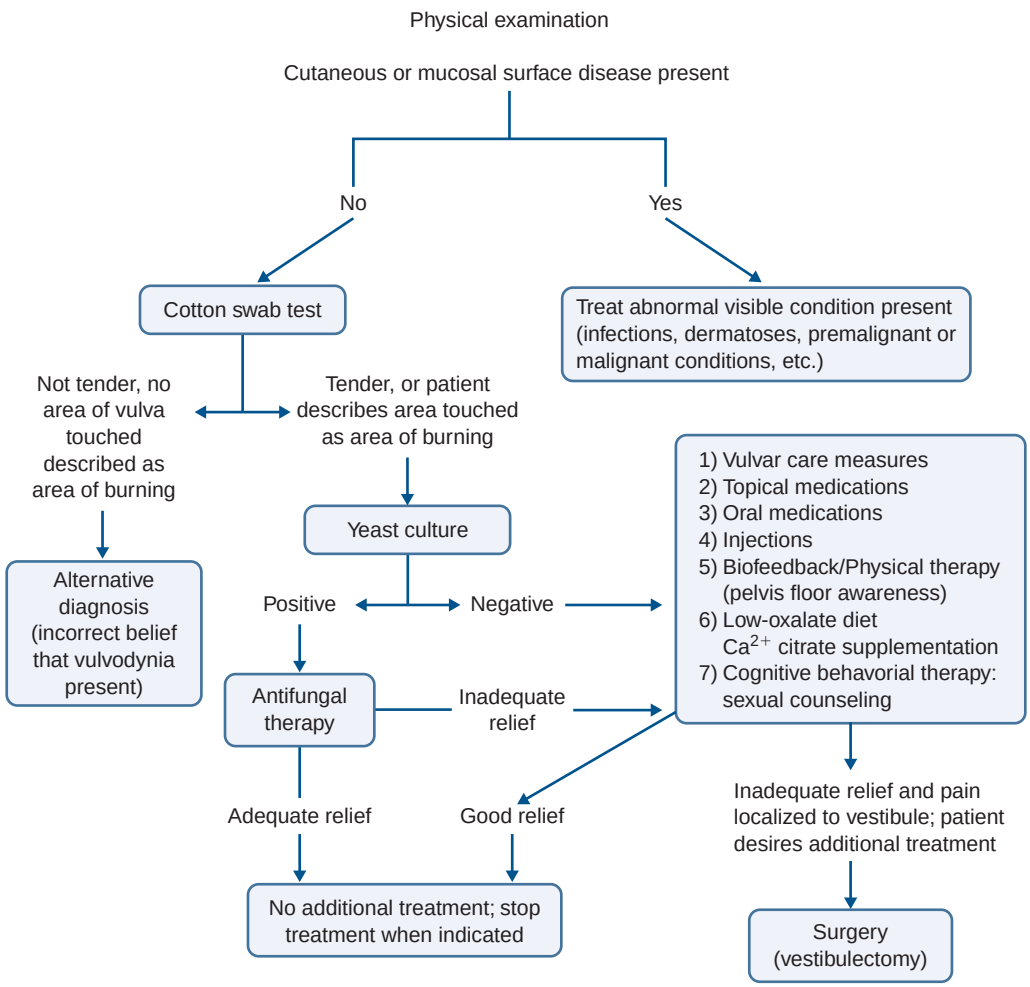

FIGURE 14.22 Vulvodynia algorithm. (From Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. *J Lower Genital Tract Dis.* 2005;9[1]:42, with permission.)

TABLE 14.11 Oral Medications Used to Treat Vulvodynia[a]

Medication Category Medication	Dosage	Side Effects
Antidepressants Amitriptyline (Elavil; AstraZeneca Pharmaceuticals LP, Wilmington, DE)	Initial amitriptyline prescription: Amitriptyline 10 mg or 25 mg. Directions: 1 by mouth each night for 1 wk; if symptoms persist, 2 by mouth each night for 1 wk; if symptoms persist, 3 by mouth each night for 1 wk; if symptoms persist, 4 by mouth nightly. Maintain nightly dose that relieves symptoms. Generally, do not exceed 100 to 150 mg nightly. Start at 10 mg in patients age 60 or older, or in patients that have not been able to tolerate higher dosages. Increase by 10 mg weekly. Often other medications should be tried in the elderly population than amitriptyline. Do not stop suddenly. Wean by 25 mg every 3 to 4 days. Discuss interaction with alcohol (no more than one drink per day). If patient is in the reproductive age group, discuss contraception.	Common reactions (amitriptyline) Dry mouth, drowsiness, dizziness, constipation, weight gain, urinary retention, tachycardia, blurred vision, confusion Serious reactions (amitriptyline) Seizures, stroke, myocardial infarction, agranulocytosis, thrombocytopenia
Nortriptyline (Pamelor; Novartis Pharmaceuticals Corp., East Hanover, NJ)	Same dosing as amitriptyline.	Common reactions Dry mouth, drowsiness, dizziness, constipation, urinary retention, tachycardia, blurred vision, weight gain, confusion Serious reactions Seizures, MI, stroke agranulocytosis, thrombocytopenia
Desipramine (Norpramin, Hoechst Marion Roussel for Aventis Pharmaceuticals, Bridgewater, NJ)	Same dosing as amitriptyline, except desipramine is often taken in the morning instead of the evening.	Common reactions Drowsiness, dizziness, blurred vision, dry mouth, constipation, tachycardia, urinary retention, diaphoresis, weakness, nervousness, rash, seizures, tinnitus, anxiety, confusion Serious reactions Seizures, sudden death, arrhythmias, stroke, myocardial infarction, atrioventricular block, thrombocytopenia
Venlafaxine (Effexor XR; Wyeth Pharmaceuticals, Madison, NY) Consider this in patients that do not respond to the common tricyclic antidepressants. Often used in conjunction with an anticonvulsant.	It is started at 37.5 mg daily (in the morning) with an increase to 75 mg daily (in the morning) after 1 to 2 weeks. Can increase gradually (dose changes every 1 to 2 weeks) to a maximum dose of 150 mg daily. When stopping the medication, wean by 75 mg/week. Well tolerated in the elderly population.	Common reactions Headache, nausea, somnolence, weight loss, anorexia, constipation, anxiety, vision changes, diarrhea, dizziness, dry mouth, insomnia, weakness, sweating, hypertension Serious reactions Seizures, suicide ideation, depression
Other antidepressants are used to treat pain. These include: fluoxetine (Prozac; Eli Lilly & Co., Indianapolis, IN); sertraline (Zoloft; Pfizer Inc., New York, NY); paroxetine (Paxil; GlaxoSmithKline, Research Triangle Park, NC); citalopram (Celexa; Forest Laboratories Inc., New York, NY)		
Anticonvulsants Gabapentin (Neurontin; Pfizer Inc., New York, NY)	Gabapentin comes in 100-, 300-, 400-, 600-, and 800-mg tablets. Generally, it is started at 300 mg by mouth daily for 3 days, then 300 mg by mouth twice daily for 3 days, then 300 mg by mouth three times daily. It can be increased gradually to 3600 mg total daily. Ideally, gabapentin is given in a three times daily dosage, but if the patient is unable to comply with that, it can be given in a twice-daily dosage. However, if using higher doses, a three times daily regimen should be followed. Do not exceed 1200 mg in a dose. For the elderly population, do not exceed 2700 mg/day.	Common reactions Somnolence, dizziness, ataxia, fatigue, nystagmus, tremor, diplopia, rhinitis, blurred vision, nausea, vomiting, nervousness, dysarthria, weight gain Serious reactions Leukopenia
Carbamazepine XR (Tegretol-XR; Novartis Pharmaceuticals Corp., East Hanover, NJ)	Start at 100 mg by mouth nightly. Add 100 mg every 3 days, titrating with blood levels. Requires serial blood tests (drug level, liver function tests, and complete blood count). For pain, the general dose is 200 to 400 mg by mouth twice daily. Maximum dose is 1200 mg/day. Comes in 100-, 200-, 400-mg tablets.	Common reactions Dizziness, drowsiness, unsteadiness, incoordination, nausea/vomiting, blurred vision, nystagmus, allergic rash, confusion, elevated liver transaminases, hyponatremia, ataxia Serious reactions Hypersensitivity reactions, seizures, arrhythmias, syncope, aplastic anemia, agranulocytosis, thrombocytopenia, leukopenia, pancytopenia, hepatitis, cholestatic jaundice, hyponatremia, water intoxication, porphyria, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, pancreatitis

TABLE 14.11 Oral Medications Used to Treat Vulvodynia[a] *(Continued)*

Medication Category Medication	Dosage	Side Effects
Topiramate (Topamax; Ortho Pharmaceutical Corp., Raritan, NJ)	Start at 25 mg daily to twice daily. If symptoms persist, 50 mg by mouth twice daily for 1 week; if symptoms persist, 75 mg by mouth twice daily for 1 week. If symptoms persist, 100 mg by mouth twice daily. Maintain at the doses above where symptoms are controlled. In the elderly and chronically ill, or those with renal or hepatic dysfunction, start at a lower dose and titrate more slowly.	Common reactions Asthenia, fatigue, paresthesia, tremor, ataxia, confusion, difficulty with concentration or attention, dizziness, breast pain, dysmenorrhea, diplopia, myopia, acute and secondary angle closure glaucoma, nystagmus, memory problems, nervousness, psychomotor retardation, somnolence, nausea, speech or language problems Serious reactions Hyperthermia, oligohidrosis, anemia (rare), leukopenia (infrequent), dyspnea (rare), hepatic failure, hepatitis, pancreatitis, renal calculi, renal tubular acidosis, hyperchloremic, nonanion gap metabolic acidosis
Other medications that have been used for vulvodynia Tramadol (Ultram; Ortho Pharmaceutical Corp., Raritan, NJ)	This is a synthetic 4-phenylpiperidine analog of codeine. Studies have shown that it is effective for long-term pain management in the elderly population. 50–100 mg by mouth every 4–6 hours. Start at 25 mg by mouth in the morning then increase by 25 mg per day every 3 days to 25 mg four times daily then increase by 50 mg/day every 3 days to 50 mg four times daily, then maintenance. Do not stop suddenly. Maximum dose is 200 mg/day in the elderly population; up to 400 mg/day may be used in the general population.	Common reactions Dizziness, nausea, constipation, headache, somnolence, vomiting, pruritus, nervousness, confusion, euphoria, tremor, spasticity, emotional lability, vasodilation, visual disturbances, urinary retention, incoordination, anorexia, rash Serious reactions Seizures, respiratory depression, anaphylaxis, angioedema, bronchospasm. Stevens-Johnson syndrome, toxic epidermal necrolysis, hypotension, orthostatic serotonin syndrome, hallucinations, suicidal ideation, dependency

MI, myocardial infarction.
[a]With all of the antidepressants discussed, adequate time for a treatment trial must be given before abandoning them, as long as the side effects are tolerable.
From Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. *J Lower Genital Tract Dis*. 2005;9(1):40–51.

Investigators have also similarly demonstrated favorable clinical responses using a variety of local therapies in a number of case series and small, uncontrolled trials. Injectable interferon, injectable steroids and lidocaine, injectable botulinum toxin, topical nitroglycerin, topical lidocaine, and topical capsaicin have shown some efficacy. Of the topical preparations, all have demonstrated promise as treatments for localized vulvodynia. For example, in a treatment trial of 5% lidocaine ointment among 61 women with vulvar pain, Zolnoun found a significant increase in patients' ability to have intercourse (76% versus 36% at baseline) and a significant decrease in intercourse-related pain.[110] A table of topical medications used to treat vulvodynia by Haefner et al.[104] may be useful when considering treatment options (Table 14.12).

The success of physical therapy and treatment interventions using vaginal surface electromyographic biofeedback, coupled with the recent evidence demonstrating increased vaginal hypertonicity, lack of vaginal muscle strength, and restriction of the vaginal opening in women with vestibulodynia, suggests that targeting pelvic floor muscle functioning can be successful in relieving the pain these patients experience with intercourse and improving sexual function.[103] Physical therapy treatment techniques include internal (vaginal and rectal) and external soft-tissue mobilization and myofascial release, trigger point pressure application, electrical stimulation, bladder and bowl retraining as well as home vaginal dilation.[104] However, compliance with this treatment option requires repeated visits and is best suited to motivated patients who wish to avoid the side effects of medical or surgical therapy.

Vestibulectomy has the highest reported clinical cure rates in excess of 80% in a number of trials, both controlled and uncontrolled, but is typically reserved for patients with localized pain who have not responded to more conservative therapy. Predictors of surgical failure include primary vestibulitis, diffuse vulvar pain, urinary symptoms, and muscle hypertonicity. Bornstein et al.[111] concluded that there are two groups of patients who will not be helped by surgical intervention: women with primary pain on intercourse and women with constant pain in addition to dyspareunia. In performing a vestibulectomy and prior to induction of either spinal or general anesthesia, the provider should carefully demarcate and outline the areas of pain to ensure complete excision.

Other less well-publicized methods of treatment such as acupuncture and hypnosis have been used to a lesser

TABLE 14.12 Topical Medications Used to Treat Vulvodynia

Topical Medication	Dosage	Side Effects[a]
5% lidocaine ointment	Apply to skin as needed; dispense 30-g tube. Do not use >20 g of ointment in a 24-h period.	Erythema or edema. Rare cases of purpura. If ointment is present on skin during intercourse, the partner may experience numbness.
EMLA cream (lidocaine 2.5% and prilocaine 2.5%; AstraZeneca Pharmaceuticals LP, Wilmington, DE)	Apply to skin prn. Do not exceed 2.5 g over 20–25 cm^2 of skin surface (e.g., a 5- × 5-cm area). Dispense 30-g tube.	Paleness, erythema, and swelling.
L-M-X 4, formerly ELA-Max 4% cream (lidocaine 4%; Ferndale, Ferndale, MI) L-M-X 5, formerly ELA-Max Anorectal 5% cream (lidocaine 5%); Ferndale, Ferndale, MI	Apply to skin as needed. Dispense 30-g tube.	Erythema and edema.
Estrogens Estrace vaginal cream (estradiol vaginal cream 0.01%); Bristol-Meyers Squibb Company, Princeton, NJ	These can be used intravaginally or topically. For treatment of vulvar and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Usual dosage: The usual dosage range is 2 to 4 g (marked on the applicator) daily for 1 or 2 weeks, then gradually taper. Tube contains 1.5 oz (42.5 g) with a calibrated plastic applicator for delivery of 1, 2, 3, or 4 g.	Common reactions Vaginal bleeding, spotting, breast changes, nausea, vomiting, headache, fluid retention, mood changes, weight changes, rash Serious reactions Thromboembolism, stroke, MI, breast, endometrial changes, fibroid enlargement, gallbladder disease, cholestatic jaundice, pancreatitis, asthma worsening, depression, hypertension
Premarin vaginal cream (conjugated estrogens 0.625 mg/g); Wyeth-Ayerst Company, Philadelphia, PA	0.5 to 2 g daily, intravaginally, depending on the severity of the condition. Taper gradually to every other day, twice weekly, etc. Patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of abnormal vaginal bleeding. Each contains net wt. 1.5 oz (42.5 g) tube with one plastic applicator calibrated in 0.5-g increments to a maximum of 2 g. Taper gradually.	
Amitriptyline 2%/baclofen 2% in water washable base (Elavil 2%/Lioresal 2% in water washable base) Elavil (AstraZeneca Pharmaceuticals LP, Wilmington, DE) Lioresal (Geigy Novartis Pharmaceuticals Corp., East Hanover, NJ)	Topical amitriptyline 2% with baclofen 2% in water washable base (WWB); squirt 0.5 mL from syringe onto finger and apply to affected area one to three times daily. Dispense 30-day supply	Common reactions (amitriptyline) Irritation, contact dermatitis, dry mouth, drowsiness, dizziness, constipation, weight gain, urinary retention, tachycardia, blurred vision, confusion Serious reactions (amitriptyline) Seizures, stroke, myocardial infarction, agranulocytosis, thrombocytopenia Common reactions (baclofen) Drowsiness, dizziness, weakness, nausea, confusion, hypotension, headache, insomnia, constipation, muscle weakness, rash, sweating, fatigue Serious reactions (baclofen) Depression, respiratory problems, ataxia, syncope, seizures, hallucinations, exacerbation of spasticity

prn, as needed; MI, myocardial infarction.
[a]Generally, the side effects of topical medications are less than when taken systemically.
From Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. *J Lower Genital Tract Dis*. 2005;9(1):40–51.

extent without any major documentation and may provide comfort for some women. Alternatively, dietary modifications (including a "low-oxalate" diet) have been widely reported with little evidence to support effectiveness.

Management of vulvar pain is a complex process, which begins with identification (diagnosis) and education. Care should follow the principles of general chronic pain management including a multidisciplinary approach based on etiologic factors and the context of the pain given the heterogeneous nature of vulvodynia. Despite limitations in the treatment of vulvodynia (there are no FDA-approved treatments for vulvodynia), practitioners should have a repertoire of management suggestions that may be of benefit including consultation and referral to other health professionals.

PEDICULOSIS PUBIS

Pediculosis pubis is caused by the pubic louse, Pthirus pubis, which may also infest other areas with hair,

including the eyelashes. It affects about 2% of the population worldwide and causes an intense itching in the pubic area. The pruritus results from an allergic reaction to the louse saliva; this reaction may become stronger over the first 2 weeks after the initial infection. In some cases, a grey-blue or slate colored macule may be seen at the feeding site, which may last for several days. Live lice or nits may often be seen by the naked eye. It is acquired through intimate contact with another individual or it may occur through fomite transmission such as towels, clothing, or beds. The louse does not survive long away from the human body. Infection in a child or teenager is not necessarily indicative of sexual abuse, although this possibility should be kept in mind. Testing for other sexually transmitted infections is recommended in most cases. Treatment includes permethrin or pyrethins with piperonyl butoxide. Lindane is a second line of therapy due to concerns around toxicity (it is not recommended in people with extensive dermatitis, pregnant or nursing mothers, or children under the age of 2 or weighing less than 50 kg, or those with uncontrolled seizures). Infection of the eyelashes may be treated with the application of petroleum jelly twice a day for 10 days or with malathion, phenothrin, and carbaryl. Bedding and clothing should be laundered and intimate contact should be avoided until the infection is cured. A second treatment may be required if the infection is not gone within 3 to 7 days. Partners from the last 30 days should be evaluated and treated if necessary.

SUMMARY

The evaluation of patients with vulvovaginal complaints begins with a thorough history and physical examination. In cases of acute vulvar pruritus, infections (most commonly, vulvovaginal candidiasis and bacterial vaginosis) and contact dermatitis should be suspected. Chronic vulvar pruritus, on the other hand, should signal a search for underlying dermatoses, such as LS, lichen simplex chronicus, or psoriasis; neoplasia (including VIN, SCC, Paget disease of the vulva); or vulvar manifestations of systemic diseases, such as Crohn disease. Patients presenting with pain should first be evaluated to rule out underlying organic causes, including inflammatory conditions, neoplasia, infections, or neurologic disorders. When organic causes are ruled out, the diagnosis of vulvodynia can be made, and attention should then be paid to more fully elucidate the nature of the pain disorder (generalized versus localized, spontaneous versus provoked).

In the evaluation of infectious causes of vulvovaginal complaints, microscopy using both saline and potassium hydroxide preparations, in conjunction with vaginal pH determination, helps guide the use of subsequent diagnostic tools, including vaginal fungal cultures, a variety of FDA-approved point of care tests, culture or PCR for confirmation of herpes simplex virus, and specific serologic tests. For autoimmune disorders and suspected cases of neoplasia, biopsy is invaluable and should be liberally employed.

Treatment, if possible, should be evidence-based, although for many vulvar disorders, such evidence has not yet been accrued. For a number of disorders, including pain syndromes, providers should be aware that often, more than one modality will be required and treatment must be individualized. Patient education in vulvar hygiene measures and avoidance of many common irritants and triggers will help reduce the risk of both developments of contact dermatitis and lichen simplex chronicus as well as exacerbation of other underlying vulvar dermatoses.

Consultation with or referral to a specialist in vulvovaginal disorders, if available, can help provide comprehensive care and optimal management. Lastly, consultation with providers in dermatology as well as selected use of other specialists, including but not limited to ophthalmologists, dentists, gastroenterologists, and rheumatologists, is often essential to the appropriate diagnosis and management of patients with more complicated disorders.

CLINICAL NOTES

- Acute pruritus is most often infectious, with allergic and irritant contact dermatitis playing a role in some cases.
- Chronic pruritus, in general, has a history of gradual onset; examples of which include lichen simplex chronicus, LS, psoriasis, and various manifestations of HPV-related disease.
- The incidence of VIN has increased significantly since the 1970s.
- Although warty-bowenoid or undifferentiated VIN is diagnosed more frequently than simplex or differentiated VIN, the latter may play a larger role in the pathogenesis of vulvar SCC.
- When using colposcopy to evaluate for VIN, it is important to remember that the vulvar area must be soaked with acetic acid for about 5 minutes. Acetowhite changes do not determine the diagnosis; rather, they only serve to indicate where biopsies should be taken.
- Because of the increased risk of a noncontiguous adenocarcinoma, if the diagnosis of vulvar Paget disease is made, the workup should

(continues)

include colonoscopy, cystoscopy, mammogram, and colposcopy.

- Treatment of contact dermatitis involves identification and elimination of the irritating agent. Topical steroids may be used for 2 to 3 weeks to reduce inflammation and promote healing.
- Lichen simplex chronicus represents an end-stage disorder resulting from long-standing irritation, endogenous eczema, allergens, or infection.
- Doxepin or hydroxyzine may be particularly helpful when antihistamines do not control pruritic symptoms, although both may be sedating.
- LS does not involve the vagina.
- LP presents in two ways: classic and erosive forms; it may involve the vagina.
- LP, LS, and psoriasis can exhibit Köbner phenomenon (i.e., the disease can flare at any site of injury, including surgical sites).
- For autoimmune disorders and suspected cases of neoplasia, biopsy is invaluable and should be liberally employed.
- The diagnosis of Bartholin cysts and abscesses is clinical and readily made on visual vulvar examination. The classic, medially protruding cystic structure at the inferior aspect of the labia (5 and 7 o'clock position) crossed by the labium minus is almost certainly a Bartholin cyst.
- Broad-spectrum antibiotic coverage is recommended for the treatment of Bartholin gland abscesses because they are typically polymicrobial.
- Of the techniques described for treatment of Bartholin cysts and abscesses, drainage with concurrent marsupialization appears to be the optimal choice in terms of technical ease, low cost, and availability of necessary equipment as well as preservation of glandular function.
- Therapeutic intervention in hidradenitis suppurativa is aimed at decreasing inflammation; treating infection; and diminishing pain, drainage, and odor.
- Hidradenitis suppurativa is thought to be caused by follicular occlusion.
- Smoking and obesity are strongly associated with hidradenitis suppurativa and may exacerbate symptoms.
- Up to 25% of estrogen replacement users will continue to experience symptoms of urogenital atrophy despite improvement in other symptoms associated with estrogen deficiency.
- Vulvodynia is defined as vulvar pain occurring in the absence of an underlying recognizable disease. The classification of vulvodynia is based on the site of the pain, whether it is generalized or localized, and whether it is provoked, unprovoked, or mixed.
- TCAs, such as amitriptyline (10 to 75 mg), have been used with some success in treating vulvodynia.
- Other treatments for vulvodynia include gabapentin, lidocaine gel, and biofeedback. Care of women with vulvodynia should follow the principles of general chronic pain management including a multidisciplinary approach based on etiologic factors and the context of the pain.

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CHAPTER 15

Urogynecology and Pelvic Floor Dysfunction

Thomas M. Julian

As the American population ages, the number of women suffering pelvic floor dysfunction increases. These disorders cause changes in normal urination, defecation, sexual function, and pelvic comfort.[1]

URINARY TRACT INFECTION

Acute Urinary Tract Infection

Acute urinary tract infection (UTI) is a common reason women seek health care. Sexually active women ages 20 to 40 years and postmenopausal women have the highest incidence of acute, uncomplicated UTI. Nearly half of women will experience one UTI in their lifetime, and half of those women will have at least one additional UTI.[2] Risk factors associated with UTI are female gender, sexual activity and spermicide-based contraception, and a history of recent UTI. After menopause, UTI may be more common because tissues of the vagina, urethra, and the base of the bladder atrophy and may serve as less of a deterrent to bacterial contamination. Postmenopausal women are also more prone to diabetes and chronic illness(es) that may impair their immune system. Kidney stones and anatomic urinary tract abnormalities (usually diagnosed in childhood) may predispose to infection as will urinary tract catheterization.[2,3]

Normally, urine is sterile and contains fluids, salts, and waste products. Infection occurs in most cases when fecal bacteria colonize the vaginal introitus and then enter the urethra and multiply. The ureters and bladder normally prevent urine from backing up toward the kidneys, and the flow of urine from the bladder helps wash bacteria out of the body. Glycoproteins line the bladder to help prevent adherence of bacteria to the bladder wall.

Symptoms and Evaluation

In most cases, lower UTI symptoms and signs develop rapidly and may include a strong, persistent urge to urinate accompanied by dysuria, frequency, small-voided volumes, hematuria, cloudy urine, and/or strong-smelling urine. The symptoms of cystitis may be subtle in the very young and the elderly. The probability of cystitis in a woman with any symptom of a UTI is 50%, and if she has dysuria and frequency without any accompanying vaginal discharge or vaginitis, it is 90%.[4] Three studies have shown that UTI can be accurately self-diagnosed by women 85 to 95% of the time and that a short-term antibiotic regimen is highly effective curative therapy.[5–7] Symptoms such as malaise, temperature elevation, chills, suprapubic tenderness, flank tenderness, and rigors suggest upper UTI.

Visual inspection of the urine is not helpful in diagnosis other than to identify gross bleeding. Cloudiness is most often due to protein or crystals and malodorous urine from diet or medication. Patients with UTI symptoms should give a clean catch urine specimen for analysis. The higher bacterial count of the first morning void makes it the preferable one for analysis. The urethra is cleansed and urine collected at midstream into a sterile container and sent as soon as possible to be examined. If the specimen will not be sent and processed within 2 hours from collection, it needs to be refrigerated at 4°C and never held for more than 48 hours.

Problems with interpreting a urinalysis because of poor collection technique (contamination) are common in the elderly or disabled and may result in either high false-positive test rates or specimens that cannot be interpreted. In these instances, urine sample collection should be assisted by a nurse or, if necessary, obtained by sterile catheterization.

A fresh specimen can be examined in office with reagent strips (dipstick test) and/or microscopic urinalysis. The dipstick test is simpler and quicker, consisting of dipping a commercially available strip into the fresh specimen. Colormetric reagent boxes on the stick are individual assays for pH, specific gravity, protein, glucose, ketone, bilirubin, urobilinogen, blood, leukocyte esterase (white blood cell [WBC]), and nitrite reductase. After predetermined developing times listed on the bottle containing the strips, the colors of the reagent boxes are compared to references on the bottle. A urine pH greater than or equal to 7.5 suggests UTI. The nitrite test is designed to detect bacteria; it detects greater than 10^5 colony-forming units (CFU)/mL of *Enterobacteriaceae* per mL of urine, although it lacks adequate sensitivity for detection of other organisms, so negative results should be interpreted with caution.[8] Leukocytes are lysed and liberate esterase when the urine pH is greater than 6.0,

when urine osmolality is low, or when analysis is delayed. Dipstick analysis is most predictive for UTI when the results are positive for bacteria (positive nitrites) and the presence of leukocyte esterase is detected; in these instances, they have a sensitivity of 75% and a specificity of 82% for UTI.[4] Some foods may produce false-positive nitrite tests. A negative dipstick, in the presence of significant UTI symptoms, does not rule out an infection and empiric therapy, or further evaluation may be warranted.

Urine microscopy from a centrifuged specimen can be used to diagnose UTI. Bacterial counts are estimated from low-power field (lpf) or high-power field (hpf) counts, and greater than 10 WBC/hpf indicate pyuria. Pyuria is present in almost all women with acute cystitis or pyelonephritis; if it is absent, an alternative diagnosis must be strongly considered.[9] The Infectious Disease Society of America has moved away from the traditional threshold of 10^5 CFU/mL as the cutoff for UTI and now recommends a criterion of greater than or equal to 10^3 CFU/mL of a typical uropathogen.[10]

Urinalysis alone is sufficient for the diagnosis of uncomplicated cystitis if the symptoms are consistent with a UTI. Urine culture and sensitivity testing are indicated for failed therapy or suspected antibiotic resistance, recurrent infection, suspected pyelonephritis, uncertain diagnosis after office evaluation, pregnancy, or patients at high risk for UTI.[11–13]

Pathology

Quantitative bacterial counts help distinguish infection from contamination, although studies show that lower bacterial counts in symptomatic women can still be important.[14] Low-count bacteriuria (10^2 and 10^4) with microorganisms typical of UTI may signal an early phase of UTI. Symptoms may start when the urethra is colonized. As a result, some think the microbiologic UTI criterion should be reduced to greater than 10^2 CFU/mL in symptomatic patients, especially when *Enterobacteriaceae* are grown. A catheterized urine specimen is considered UTI positive with a growth of 10^2 CFU/mL. In children, UTI is defined as a bacterial count approximately 10^4 CFU/mL urine, excluding vaginal contamination of the specimen. For infections with *Staphylococcus saprophyticus* and *Candida* species, the lower cutoff is greater than 10^4 CFU/mL.

Approximately 70 to 90% of UTIs are caused by strains of *Escherichia coli*. Approximately 5 to 15% of UTIs are caused by *Staphylococcus saprophyticus*. Other causative organisms include *Aerobacter aeruginosa*, *Klebsiella*, *Proteus* and *Pseudomonas*, and the more difficult to detect *Haemophilus influenzae* and *Haemophilus parainfluenza*, which do not grow well in culture media for enteric bacteria. Other problematic microorganisms include acid-fast bacilli, *Campylobacter*, *Corynebacterium*, *Legionella*, *Pneumococcus*, *Salmonella*, *Shigella*, fungi (*Blastomyces* and *Coccidioides*), *Neisseria gonorrhoeae*, *Chlamydia*, and *Herpes simplex*. DNA tests, Gram stain, and acid-fast stains should be performed for those with UTI symptoms, pyuria, and negative culture.[15]

Asymptomatic Bacteriuria

Asymptomatic bacteriuria refers to isolation of the same organism in bacterial counts greater than or equal to 10^5 CFU/mL in two consecutive clean catch urine samples in a patient without UTI symptoms.[16] Some studies define it as a single positive urine specimen with greater than or equal to 10^5 CFU/mL, but transient bacteriuria is common in healthy young women, so the requirement for more than one positive specimen for diagnosis may more accurately reflect the true prevalence.[17] If the patient is catheterized, asymptomatic bacteriuria is defined as a single catheterized specimen with isolation of a single organism in quantitative counts of greater than 10^2 CFU/mL.[16]

The prevalence of asymptomatic bacteriuria increases with age, from about 1% among young girls to greater than 20% among women older than the age of 80 years who live in the community.[17,18] Among diabetic women, the prevalence of asymptomatic bacteriuria is 8 to 14% and is related to the duration of disease and presence of long-term complications, and not necessarily any metabolic parameters of diabetes.[19]

Screening for and treating asymptomatic bacteriuria should be done for pregnant women and for patients who will undergo a urologic procedure where mucosal bleeding is anticipated.[16] It is not indicated for the following populations: women (premenopausal, nonpregnant), diabetic patients, the elderly, or patients with spinal cord injury or indwelling urethral catheters because treatment in these cases may contribute to the development of antimicrobial resistance.[20] Although women with asymptomatic bacteriuria are at increased risk for UTI, treatment does not reduce the frequency of UTIs or recurrent asymptomatic bacteriuria.[17] Although antibiotics may sterilize the urine in cases of asymptomatic bacteriuria, it generally recurs and it is not associated with long-term complications such as hypertension, renal failure, or increased mortality.[18,21]

Treatment

Once the diagnosis of UTI is confirmed, treatment should begin without delay. Antibiotics are the mainstay of treatment, but ancillary measures to provide comfort until antibiotics clear the infection include drinking plenty of water to dilute urine and irrigate the bacteria; avoiding bladder irritants such as caffeinated beverages, alcohol, and citrus-containing juices/sodas/fruits; a heating pad on the abdomen; and urinary analgesics (phenazopyridine [generic] or Urised).[22]

Antibiotics for the nonpregnant patient consist of 1- to 7-day courses of one of several medications (Table 15.1).

TABLE 15.1 First-Line Therapy for Uncomplicated Urinary Tract Infections

Drug	Dose	Comments
Trimethoprim/sulfamethoxazole (Bactrim, Bactrim DS)	160/800 mg orally, twice daily	Can be a single-dose treatment, but a 3-day course has the best treatment success; it should not be used empirically if local resistance prevalence >20% or if the patient has taken it for UTI in preceding 3 months unless the organism is known to be susceptible.
Nitrofurantoin (Macrodantin, Macrobid)	100 mg orally, twice daily for 5–7 days	Not for use if there is a suspicion of pyelonephritis or in patients with a creatinine clearance <60 mL/minute

DS, double strength; UTI, urinary tract infection.
Data from Gupta K. Emerging antibiotic resistance in urinary tract pathogens. *Infect Dis Clin North Am.* 2003;17:243–259; Metlay JP, Strom BL, Asch DA. Prior antimicrobial drug exposure: a risk factor for trimethoprim-sulfamethoxazole-resistant urinary tract infections. *J Antimicrob Chemother.* 2003;51:963–970; Gupta K, Hooton TM, Roberts PL, et al. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med.* 2007;167:2207–2212; McKinnell JA, Stollenwerk NS, Jung CW, et al. Nitrofurantoin compares favorably to recommended agents as empirical treatment of uncomplicated urinary tract infections in a decision and cost analysis. *Mayo Clin Proc.* 2011;86:480–488.

Fluoroquinolone antibiotics historically were reserved for resistant or recurrent infections or when sensitivity testing indicated they were the best choice, but antibiotic-resistant organisms have led to widespread use of these medications, especially ciprofloxacin. Most clinical symptoms of uncomplicated cystitis or pyelonephritis will respond to antibiotics within 48 hours. If symptoms persist after 48 to 72 hours or if recurrent symptoms appear in a few weeks, a more thorough evaluation for complicated infection should be undertaken.[22,23] Simple UTI does not require any follow-up cultures if symptoms resolve with antibiotics.

Recurrent Urinary Tract Infection

The diagnosis of recurrent UTI is reserved for patients who experience greater than or equal to two UTIs in 6 months or greater than or equal to three within 12 months. Most recurrences are thought to represent reinfection and not just relapse. Most recurrences occur in the first 3 months after the initial infection.[24] If the first infection is caused by *E. coli*, the likelihood of a second UTI developing within 6 months is higher compared to those cases where the first UTI was due to another organism.[25] A number of factors appear to be associated with an increased risk for recurrent UTIs.

Prophylactic antibiotic treatment is highly effective in decreasing the risk for recurrent UTI and is recommended for women with two or more symptomatic UTIs within 6 months or three or more within 12 months. Low-dose antibiotics are taken continuously for 6 months or more (see Table 15.2 for prophylactic treatment regimens for women with recurrent UTI). Nitrofurantoin or trimethoprim/sulfamethoxazole (TMPS) once daily offers excellent prophylaxis against *E. coli* with lesser risk of yeast overgrowth in the vagina with TMPS. Nitrofurantoin may not be used in patients with renal insufficiency and there are some concerns with long-term exposure and associated pulmonary reactions, chronic hepatitis, and neuropathy. Women using fluoroquinolones for prophylaxis must employ effective contraception because these are contraindicated in pregnant women and children. Other adverse events associated with fluoroquinolones include prolonged QTc interval and ruptured Achilles tendons.[26,27]

Cystitis rarely leads to kidney damage, therefore invasive testing with cystoscopy, intravenous pyelography, tomography, special scans, and renal ultrasound are not usually required prior to starting antibiotic prophylaxis for recurrent UTI. Testing is recommended for children, the elderly, and for those who fail a trial of antibiotic prophylaxis. When recurrences are frequent or a UTI becomes chronic, referral to a urologist or nephrologist for evaluation is recommended.[28]

Recommended preventive measures for UTI include making sure the patient wipes from front to back after urination or defecation to prevent bacterial contamination, emptying the bladder soon after intercourse, and avoiding chemical irritants to the area such as bubble bath, feminine deodorants, douches, or powders.

Cranberries, blueberries, and lingonberries are fruits containing tannins (proanthocyanidins), which do not treat but may prevent *E. coli* bacteria from adhering to

TABLE 15.2 Antimicrobial Prophylaxis Regimens for Women With Recurrent Urinary Tract Infection

Continuous Prophylaxis Regimens	
Trimethoprim/sulfamethoxazole	40 mg/200 mg once daily 40 mg/200 mg three times weekly
Trimethoprim	100 mg once daily
Nitrofurantoin	50 mg once daily 100 mg once daily
Cefaclor	250 mg once daily
Cephalexin	125 mg once daily 250 mg once daily
Norfloxacin	200 mg once daily
Ciprofloxacin	125 mg once daily
Postcoital Regimens	
Trimethoprim/sulfamethoxazole	40 mg/200 mg or 80 mg/400 mg
Nitrofurantoin	50 mg or 100 mg
Cephalexin	250 mg
Ciprofloxacin	125 mg
Norfloxacin	200 mg
Ofloxacin	100 mg

cells in the urinary tract, thereby inhibiting infection. These compounds do not prevent infection by urinary acidification as is commonly believed. Although some studies show cranberry juice may help decrease the number of symptomatic UTIs, the data has not definitively demonstrated efficacy, although there is little likelihood of harm in its use for this purpose.[29,30] Some research leads to the recommendation of drinking at least one to two cups of cranberry juice daily or taking at least 300 to 400 mg in tablet form twice daily.[30]

Probiotics and lactobacilli are beneficial microorganisms that may protect against infections in the genital and urinary tracts. The best-known probiotics are the lactobacilli strains, such as *acidophilus*, which is found in yogurt, fermented milk products, and dietary supplements. Other probiotics include *Bifidobacterium* and the lactobacilli *rhamnosus*, *casei*, *plantarum*, *bulgaricus*, and *salivarius*, and also *Enterococcus faecium* and *Streptococcus thermophilus*. Not all studies show benefit for probiotics in UTI, and the use of these should be considered investigational.[31]

Acute Nonobstructive Pyelonephritis

Acute uncomplicated pyelonephritis involves the same bacteria as those seen in acute UTI. Pyelonephritis often presents with sudden chills, high fever, and gastrointestinal (GI) upset. In the elderly, it may present as sudden illness, delirium, and/or vascular failure. Pyelonephritis may be managed on an outpatient basis in patients with mild to moderate symptoms who respond well with rehydration and antibiotics over a 12-hour observation period in an outpatient facility. Hospitalization is indicated in instances of severe illness with high fever, pain, debilitation, and an inability to take oral hydration or medications, pregnancy or in instances where adherence to therapy as an outpatient is questionable.

Fluoroquinolones are the only oral antibiotics recommended for the outpatient empirical treatment of acute uncomplicated pyelonephritis.[32] In cases where the likelihood of fluoroquinolone resistance is less than 10% (i.e., the community prevalence of resistance is less than 10% and the patient has not travelled to an area with endemic prevalence greater than 10% and the patient has not used a fluoroquinolone in the preceding 3 to 6 months), then empiric therapy such as ciprofloxacin 500 mg orally twice daily for 7 days or 1000 mg extended release once daily for 7 days or levofloxacin 750 mg orally once daily for 5 to 7 days may be started.[33,34] This empiric therapy may be started with or without an initial intravenous dose of antibiotics.[35,36] If there is hypersensitivity to fluoroquinolones or known resistance, therapy may include TMPS or an oral beta-lactam if the organism is known to be susceptible. If susceptibility data is not available, an initial intravenous dose of a long-acting parenteral antibiotic such as ceftriaxone or a 24-hour period of aminoglycoside use should be given.

Most clinical symptoms of uncomplicated pyelonephritis will respond to antibiotics within 48 hours and, as with uncomplicated cystitis, a follow-up culture is not indicated if symptoms resolve with antimicrobial therapy.

Other Conditions That May Mimic Urinary Tract Infection

Women with UTI symptoms may have another condition causing their symptoms, such as vaginitis, urethritis, interstitial cystitis, dermatitis, or sexually transmitted infections (STIs). Common vaginal infections caused by *Trichomonas*, *Candida*, or an anaerobic bacterial milieu may mimic a UTI. Women with painful urination whose urine does not show bacterial growth in culture may have a sexually transmitted urethritis, most commonly *Chlamydia trachomatis*. Interstitial cystitis is a bladder wall inflammation occurring predominantly in women that may elicit symptoms of a UTI. Disorders in children that mimic UTI include reactions to bubble bath, diaper rash, poor hygiene, and pinworm infestation.

FEMALE URINARY INCONTINENCE

Urinary incontinence (UI), defined by the International Continence Society (ICS), is involuntary loss of urine.[37] Most current population-based studies of UI estimate 25 to 45% of women have UI and the incidence increases with age.[38] Known risk factors for UI include childbearing, obesity, other urinary symptoms, and functional impairment. UI is common in persons with cognitive impairment, and the presence of cognitive impairment itself is associated with a 1.5- to 3.5-fold increase in the risk of UI.[39] The severity of incontinence (frequency and volume) also increases with age.[40]

UI is common during pregnancy and is estimated to affect 30 to 60% of pregnant women.[41] In the postpartum period, 6 to 35% of women report incontinence; about 50% of the women report only mild leakage, and spontaneous resolution is seen in about 70% of cases.[41]

Women with UI may experience embarrassment, depression, loss of self-esteem, sexual dysfunction, loss of productivity, and social isolation from this problem, but over half may never seek care for their symptoms, even if these occur at least once a week.[42,43] Because the prevalence of UI is high among women across the life span and many will not spontaneously bring it up with their providers, women should be specifically screened for UI.[44] Often, patients feel UI as a natural part of aging or are unaware that treatments exist, but because incontinence may serve as the signal for a serious, underlying condition such as neurologic disease or even malignancy, it should never be viewed as just an inconvenience of getting older.

Medical morbidities associated with UI include genital candidal infections, cellulitis and/or pressure ulcers, UTIs and urosepsis due to urinary retention or

indwelling catheters, falls and fractures if the woman slips on floor wet with urine, and sleep deprivation if nocturia is present. Other comorbid conditions, medications, and factors influencing patient function may cause or even worsen UI, either transiently or chronically (see Table 15.3 for potential causes or contributors to UI).

The onset and progression of UI, and its attendant psychological stress, is associated with an increased risk of comorbid psychiatric disorders including panic disorder and depression.[45,46] The onset of panic disorders is directly proportional to the extent that incontinence alters a patient's lifestyle, and the incidence of depression is related to the degree of incontinence. The greatest rate of depression is among patients with mixed incontinence.[47,48]

The annual direct cost of female UI in the United States is an estimated $12.4 billion, and the majority of those costs are borne by those living in the community ($10.8 billion) compared to women residing in nursing homes ($5.5 billion).[49,50] The vast majority of those costs are for routine care (70% of total costs) with only 9% being spent on treatments. Most of the routine costs are borne out of pocket by the women and are not reimbursed by third-party payers.

TABLE 15.3 Identification and Management of Reversible Conditions That Cause or Contribute to Urinary Incontinence

Condition	Management
Affecting the lower urinary tract	
Urinary tract infection (symptomatic with frequency, urgency, dysuria, etc.)	Antimicrobial therapy; consider topical estrogen for postmenopausal women with recurrent urinary tract infections.
Atrophic vaginitis/urethritis	Topical estrogen may worsen symptoms of incontinence, although topical estrogen may relieve atrophic vaginitis.
Pregnancy/vaginal delivery/episiotomy	Behavioral intervention; avoid surgical therapy postpartum because condition may be self-limiting.
Stool impaction	Disimpaction; appropriate use of stool softeners, bulk-forming agents, and laxatives if necessary; implement high-fiber intake, adequate mobility, and fluid intake.
Increased urine production	
Metabolic (hyperglycemia, hypercalcemia)	Improved control of diabetes mellitus or treatment of hypercalcemia
Excess fluid intake	Reduction in intake of excess fluids, especially diuretic fluids (e.g., caffeinated beverages, including soda and alcohol)
Volume overload	
Venous insufficiency with edema	Support stockings, leg elevation, sodium restriction, diuretic therapy
Heart failure	Medical therapy
Impaired ability or willingness to reach a toilet	
Delirium	Diagnosis and treatment of underlying causes of acute confusional state
Chronic illness, injury, or restraint that interferes with mobility	Address cause of impaired mobility; remove restraints if possible. Regular toileting; use of toilet substitutes and environmental alterations (e.g., bedside commode, urinal)
Psychological	Appropriate pharmacologic and/or nonpharmacologic treatment
Nocturia	
Nocturnal polyuria	Assess evening fluid intake; assess for volume overload; consider sleep apnea if other symptoms, signs, or risk factors present.
Sleep disturbance	Sleep hygiene; assess for pain, depression, and environmental causes; consider sleep apnea if other symptoms, signs, or risk factors present.

From DuBeau CE. Treatment of urinary incontinence. http://www.uptodate.com. Updated October 2011. Accessed December 2, 2013.

Incontinence Symptoms of Female Urinary Tract

Urinary Incontinence Symptoms

The International Urogynecology Association (IUGA) and ICS have categorized UI disorders by symptoms[37] (Table 15.4).

- **Stress urinary incontinence (SUI)** is involuntary UI with effort or physical exertion, such as sneezing, coughing, or activity, although it may occur without provocation if there is significant damage to the urethral sphincter. SUI occurs when an increase in intra-adominal pressure overcomes the urethral sphincter mechanisms that keep the sphincter shut; hence, there is a loss of urine in the absence of a bladder contraction. This is the most common cause of UI in younger women and often coexists with urge incontinence in middle-aged or older women.[51]
- **Urgency urinary incontinence (UUI)** is the involuntary loss of urine associated with a strong urge to void, even when the bladder is not full. Its etiology is presumed to be uninhibited bladder contractions, also referred to as detrusor overactivity.[52] This is most likely not the only etiology, however, because detrusor overactivity may be found in continent individuals as well.

TABLE 15.4 Differential Diagnosis of Urinary Incontinence

Stress urinary incontinence
  Hypermobility (anatomic)
  Intrinsic sphincter deficiency
Overactive bladder
  Motor urge incontinence
  Sensory urge incontinence
  Detrusor dyssynergia
  Detrusor hyperreflexia
  Detrusor hyperactivity with incomplete contractility
Mixed incontinence
Bypass of the continence mechanism
  Fistula
  Diverticulum
  Ectopic ureter
Overflow incontinence
Functional

- **Mixed urinary incontinence (MUI)** is involuntary UI associated with urgency and also with physical exertion; it is believed to occur when there is coexisting urgency and stress incontinence.
- **Nocturnal enuresis** is involuntary urine loss during sleep.
- **Continuous UI** is continuous involuntary urine loss and may be seen with either bladder outlet obstruction and/or impaired detrusor contractility. Patients may be unaware of the leakage at all. Although referred to as "overflow incontinence" in the past, the preferred term mentioned earlier is best to use along with any known associated pathophysiology.
- **Postural UI** is involuntary loss of urine associated with change of body position (rising from a seated or lying position).
- **Insensible UI** is when UI occurs but the woman is unaware of how it occurred.
- **Coital UI** is UI with coitus, occurring with penetration or intromission or UI occurring at orgasm.

Bladder Storage Symptoms

Bladder storage symptoms that may or may not be associated with UI include more frequent urinations during waking hours than before; although seven episodes of voiding during waking hours is often considered the upper limit of normal, it may be higher in some populations. Other symptoms related to bladder storage issues include nocturia, the interruption of sleep one or more times a night to urinate, or a significant and sudden urgency to void.[37]

Sensory Symptoms

Sensory symptoms encompass a departure from normal sensation(s) or function during bladder filling. Most individuals are aware of their bladders filling up, ultimately resulting in a strong desire to void. With increased bladder sensation, the patient is able to postpone voiding, unlike the urgency sensation associated with UUI where the patient is not able to postpone voiding. Other situations may involve a reduced bladder sensation, that is, the patient is aware the bladder is filling but the strong desire to void does not occur until later than it had in the past. Some patients may complain of absent bladder sensation and are both unaware of the bladder filling and lack any definite desire to void.[37]

Voiding Symptoms

Voiding symptoms are any departure from normal sensation or function experienced by the woman during or following urination. These include symptoms of hesitancy, slow stream, intermittent flow, straining to void, spraying or splitting of the urinary stream, incomplete bladder emptying, immediate need to void again after passing urine, needing to assume a specific position to void spontaneously or improve bladder emptying, dysuria, and urinary retention despite persistent effort to void.[37]

Initial Evaluation of Female Urinary Incontinence

Complete History and Physical Examination

The history should focus on the onset and course of incontinence and any associated symptoms. Information regarding how frequently the incontinence occurs, the amount of urine lost, the timing of the incontinence, and precipitants to the incontinence should be noted. The patient should be asked about her bowel and sexual function, the status of any other medical conditions and symptoms she may have, the use of all medications (including over the counter), and any previous surgeries, including any treatment(s) for incontinence and the outcome. A dietary review, including liquids, should be done (Table 15.5).

In general, urgency symptoms are sensitive and specific for the diagnosis of urge incontinence and a report of such symptoms is a fairly reliable diagnostic tool.[53,54] Symptoms associated with stress are fairly reliable but are not very specific in identifying SUI because they may also occur with detrusor overactivity or incomplete bladder emptying.[53]

Symptoms of slow, hesitant, or interrupted voiding patterns, straining to void, nocturia, and frequency are not diagnostically specific. Nocturia may be due to nocturnal polyuria, sleep disturbances, or a lower urinary tract issue such as detrusor overactivity.

Patients with incontinence should optimally have a comprehensive physical examination. The cardiovascular examination should note if there is any evidence of fluid overload. The abdomen should be examined for any masses or tenderness. The extremities should be examined for mobility, function, and evidence of peripheral edema.

The pelvic examination should include a close inspection of the genitalia and vaginal vault for signs of atrophy, stenosis, or inflammation. The urethra is examined for diverticulum or fistula. Urethra and bladder palpation is done to assess for a mass or tenderness. Pelvic floor muscle function is assessed visually and digitally including tone, muscle strength (static and dynamic), voluntary muscle relaxation (absent, partial, complete), muscular endurance (ability to sustain maximal or near maximal force), repeatability (the number of times a contraction to maximal or near maximal force can be performed), duration, coordination, displacement, and configuration. Assessment is bilateral, looking for unilateral defects and asymmetry.[55] Urethral hypermobility may be visually assessed by asking the woman to perform a Valsalva maneuver, although it may be hard to determine due to body habitus or a large cystocele. In these cases, urethral hypermobility can be evaluated by placing a cotton-tipped wooden-tailed applicator, lubricated with sterile 2% lidocaine

TABLE 15.5 Medications That May Cause or Worsen Urinary Incontinence

Medication	Effect on Continence
Alcohol	Frequency, urgency, sedation, delirium, immobility
α-Adrenergic agonists	Outlet obstruction (men)
α-Adrenergic blockers	Stress leakage (women)
Angiotensin-converting enzyme inhibitors	Associated cough worsens stress and possibly urge leakage in persons with impaired sphincter function.
Anticholinergics	Impaired emptying, retention, delirium, sedation, constipation, fecal impaction
Antipsychotics	Anticholinergic effects plus rigidity and immobility
Calcium channel blockers	Impaired detrusor contractility and retention; the dihydropyridine agents can cause pedal edema, leading to nocturnal polyuria.
Estrogen	Worsens stress and mixed leakage in women
GABAnergic agents (gabapentin, pregabalin)	Pedal edema causing nocturia and nighttime incontinence
Latanoprost	Urge incontinence
Loop diuretics	Polyuria, frequency, urgency
Narcotic analgesics	Urinary retention, fecal impaction, sedation, delirium
Nonsteroidal anti-inflammatory drugs	Pedal edema causing nocturnal polyuria
Oral contraceptives[a]	Stress, urge, and mixed incontinence
Sedative hypnotics	Sedation, delirium, immobility
Thiazolidinediones	Pedal edema causing nocturnal polyuria
Tricyclic antidepressants	Anticholinergic effects, sedation
Cholinesterase inhibitors	Alone may increase incontinence; increased functional impairment when combined with anti-incontinence antimuscarinic agents
β-Blockers	Urge incontinence
Opioid analgesics	Sedation, anticholinergic effects
H_1-receptor antagonists	Confusion
Lithium	Polyuria

GABA, gamma-aminobutyric acid.
[a]Townsend MK, Curhan GC, Resnick NM, et al. Oral contraceptive use and incident urinary incontinence in premenopausal women. *J Urol.* 2009;181:2170.
Reprinted with permission from DuBeau CE. Urinary incontinence. In: Pompei P, Murphy JB, eds. *Geriatrics Review Syllabus: A Core Curriculum in Geriatric Medicine.* 6th ed. New York: American Geriatrics Society; 2006:185. Table based on data from Resnick NM. Geriatric medicine. In: Isselbacher JK, Braunwald E, Wilson JD, et al, eds. *Principles of Internal Medicine.* New York: McGraw-Hill; 1994:34.

gel, into the cleansed urethral meatus to the level of the urethrovesical junction (UVJ) and asking the patient to strain (Q-tip test). The straining angle of the arm of the tail compared with the horizontal axis is the measurement of urethral or bladder neck mobility. A straining angle greater than 30 degrees is indicative of poor anatomic support of the UVJ and urethral hypermobility but does not necessarily confirm the diagnosis of SUI.

The pelvic support system should be assessed by a split-speculum exam: Remove the top blade of the speculum and hold the bottom blade firmly against the posterior vagina while asking the woman to cough (or perform a Valsalva maneuver) and look for evidence of urethral hypermobility or an anterior wall support defect during the cough. Although loss of any urine associated with these efforts is noted as a positive cough stress test and is helpful in confirming stress leakage, a negative test is less useful because it may occur from patient inhibition or an insufficient amount of urine in the bladder.[53] The posterior blade should then be placed anteriorly and held firmly while the posterior vaginal wall is inspected during a cough (or Valsalva maneuver) for evidence of loss of wall support. Bimanual examination should be performed to detect coexistent adnexal or uterine pathology.

Patients should be screened for depression and their cognitive function, as well as functional status, should be noted. The neurologic exam should assess gait, balance, and neurologic signs or symptoms indicative of cervical spondylosis or stenosis, Parkinson disease, multiple sclerosis, peripheral neuropathy, and other neurologic diseases. Vibration and peripheral sensation should be assessed for peripheral neuropathy. The T10 to S4 nerve roots are primarily responsible for voiding control, and neurologic screening should assess lumbosacral spinal segments, including asymmetry of large muscle groups or deformity of the extremities as indirect evidence of bladder function. Motor function can be assessed by flexion and extension maneuvers against resistance at the ankle, knee, and hip. Normal sensation in the upper leg and perineal dermatomes helps confirm intact sensory innervation of the lower urinary tract (Figs. 15.1 and 15.2). Patients with extensive osteoarthritis may suffer from cervical spondylosis or stenosis, which may result in

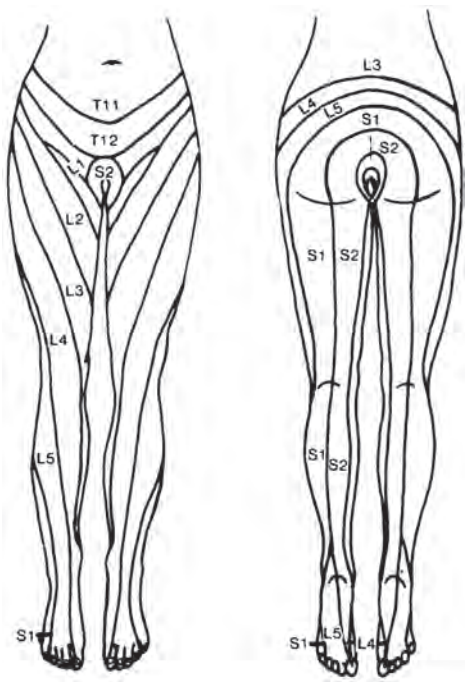


FIGURE 15.1 Dermatome map of lower extremities. (From Ostergard DR, Bent AK. *Urogynecology and Urodynamics: Theory and Practice.* 4th ed. Baltimore: Lippincott Williams & Wilkins; 1996:682, with permission.)

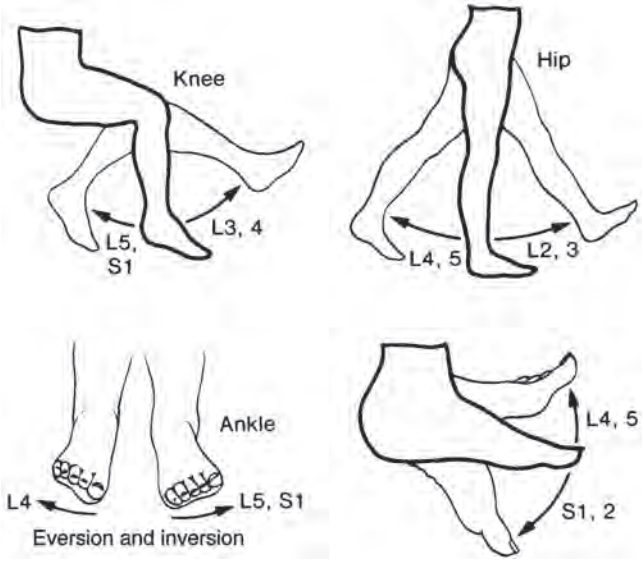


FIGURE 15.2 Testing of motor strength. (From Ostergard DR, Bent AK. *Urogynecology and Urodynamics: Theory and Practice*. 4th ed. Baltimore: Lippincott Williams & Wilkins; 1996:682, with permission.)

detrusor overactivity; examination of such patients should include assessment of lateral rotation and flexion of the neck, inspection of the hands for interosseous muscle wasting, and determination if a Babinski reflex is present because these would suggest cervical changes and resultant nerve impairment.

Neurologic evaluation of the genital/pelvic area should include an evaluation of perineal sensation and checking for reflex contraction of the pelvic floor in response to light stroking of the perineal skin lateral to the anus (anal wink) or clitoris (bulbocavernosus reflex); positive responses provide evidence of the integrity of the sacral reflex center. Rectal exam should assess sphincter tone and rule out fecal impaction, which is often associated with UI in the elderly. Vibration and peripheral sensation should be evaluated as a means of assessing for peripheral neuropathy. Findings suggestive of neurologic deficits should be referred for formal neurologic evaluation.

Noninvasive Evaluations of Urinary Incontinence

A urinalysis should be performed for all patients complaining of UI or other symptoms. In older patients, results must be interpreted carefully because there is a high prevalence of asymptomatic bacteriuria in this population; this is not a cause of incontinence.

Pelvic floor questionnaires evaluate the impact of pelvic floor disorders on urinary, bowel, comfort, and sexual function and may help determine the magnitude of the problem for the patient in a way that helps the provider. Having the patient identify the aspect of her incontinence that causes her the most difficulty, either spontaneously or through a questionnaire, may help to target or possibly prioritize treatment approaches. In the United States, some of the questionnaires commonly used include Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12), Incontinence Impact Questionnaire (IIQ), Urogenital Distress Inventory (UDI), and the Overactive Bladder Treatment Satisfaction Questionnaire (OAB-S).[56] The 3IQ test has been developed as a simple means of distinguishing between stress and urge incontinence (Fig. 15.3).[57]

Asking the patient to keep a bladder diary, or urolog, may be clinically helpful, especially for issues of nocturia, high urinary frequency and/or incontinence frequency, or when the history is unclear. Patients are given a urolog and instructions on what information needs to be recorded as well as how to record the information and a measuring container that fits over the toilet bowl (Fig. 15.4). She records the time and volume/type of her fluid intake and spontaneous voids over a 24- to 72-hour time period (this does not have to be consecutive) while also recording her activities. Additional information regarding prevoid urgency, incontinent episodes (and estimated amounts, e.g., drops, small, medium, and soaking), activity precipitating incontinence, pad usage, episodes of urgency, and abnormal sensation may also be recorded. Although reliability is greatest with the use of 7-day diaries, these can be difficult to keep so it is quite common to use 2- or 3-day diaries in both clinical and research settings.[58] Typically, eight voids or fewer during the day are considered normal, and nocturnal frequency should be no more than two times during the night. Polydipsia should be considered when fluid intake exceeds 40 mL/kg body weight during 24 hours, and nocturnal polyuria occurs when over 20 to 30% of total daily fluid volume ingested is voided at night.

Quantification of the amount of urine lost during incontinence episodes may be done by measuring the increase in the weight of perineal pads that are weighed pre- and post-testing. This gives a guide to the severity of incontinence. The pads may be worn over a short period such as 1-hour or 1- to 2-day test periods, and the patient may partake in a variety of activities ranging from normal everyday ones to provocation with defined stress regimens. The perineal pad test, with or without a urinary dye, also is useful to assess urine loss when the patient does not know whether the fluid being lost is urine. The patient wears the pad, and the pad is observed (when dye is used to color urine) or weighed.

Urologic Testing

Although one often sees the word "urodynamics" to describe this testing, there is no predetermined, all-inclusive combination of tests that is described by this term. Urodynamics testing is based on the premise that any situation where intravesical pressure is higher than

1. During the last 3 months, have you leaked urine (even a small amount)?

☐ Yes ☐ No → *Questionnaire completed*

2. During the last 3 months, did you leak urine:
(Check all that apply)

☐ a. When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?
☐ b. When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?
☐ c. Without physical activity and without a sense of urgency?

3. During the last 3 months, did you leak urine *most often*:
(Check only one)

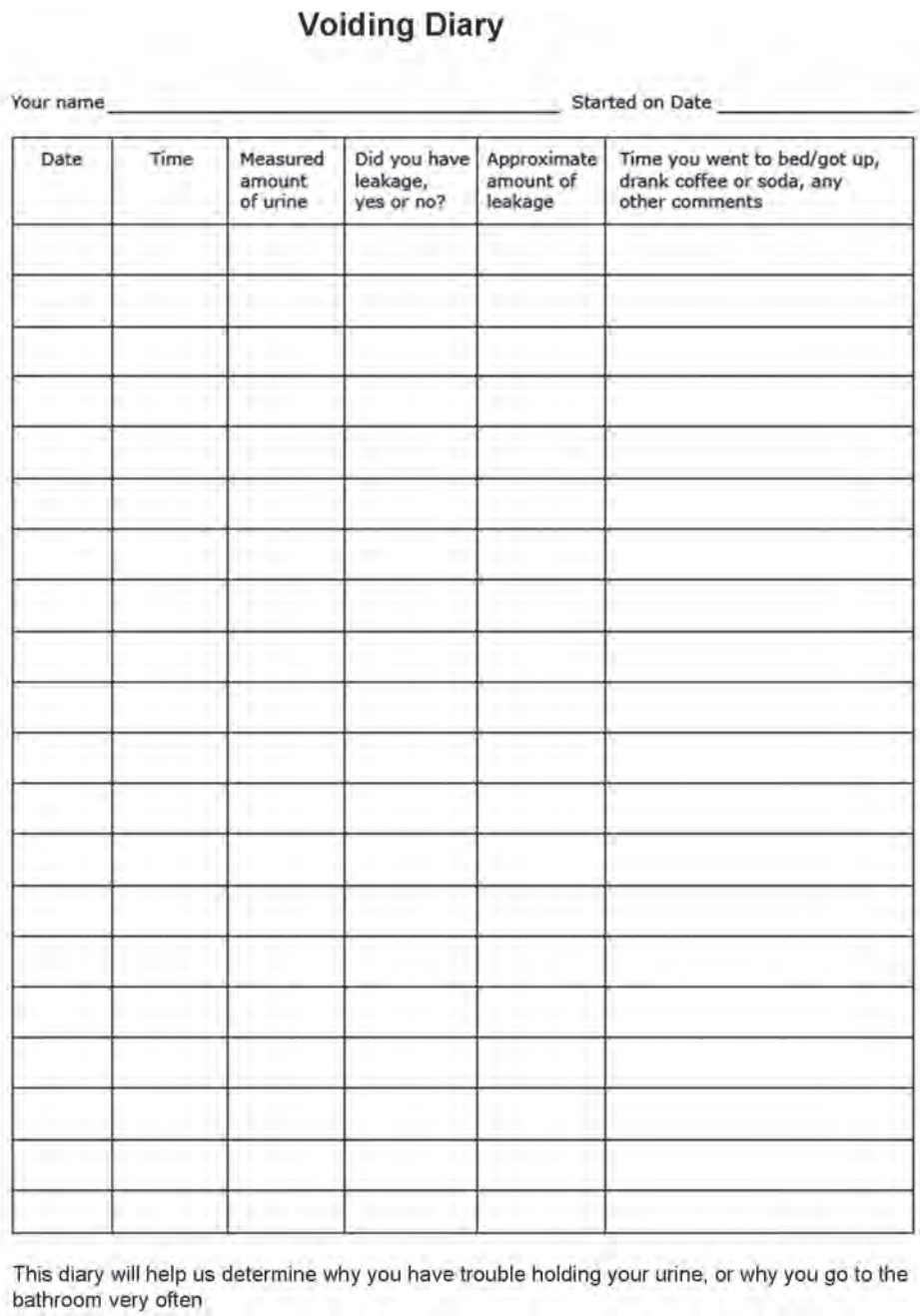
☐ a. When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?
☐ b. When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?
☐ c. Without physical activity and without a sense of urgency?
☐ d. About equally as often with physical activity as with a sense of urgency?

Definitions of type of urinary incontinence are based on responses to question 3:

Response to question 3	Type of incontinence
a. Most often with physical activity	Stress only or stress predominant
b. Most often with the urge to empty the bladder	Urge only or urge predominant
c. Without physical activity or sense of urgency	Other cause only or other cause predominant
d. About equally with physical activity and sense of urgency	Mixed

FIGURE 15.3 The 3 incontinence questions. (Reproduced with permission from Brown JS, Bradley CS, Subak LL, et al. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. *Ann Intern Med.* 2006;144:715. Copyright © 2006 American College of Physicians.)

urethral closure pressure will result in urinary leakage, and this can be due to either decreases in urethra closure pressure caused by urethral dysfunction or increases in bladder pressure caused by detrusor dysfunction or a combination of both. There are a multitude of clinical tests measuring various properties of the lower urinary tract that have been developed—from simple office cystometrics to multichannel video studies.[37,59] For many, urodynamic testing has become routine practice, but its role in the evaluation of incontinence for all is controversial. It is expensive, requires specialized equipment and training, does not always correlate with symptoms, and is invasive (Table 15.6).[60,61] Although it is associated with about a 2% risk of UTI, prophylactic antibiotics are not necessary.[62] Studies trying to demonstrate better treatment outcomes in instances of UI based on urodynamic testing results compared to treatment based on history and physical examination alone have been mixed.[63,64] One meta-analysis that included 1000 women with clinical symptoms of stress incontinence showed that when compared against a urodynamic diagnosis, testing was 91% sensitive but only 51% specific in diagnosing pure stress incontinence. The same analysis showed that for urge



Voiding Diary

Your name _____ Started on Date _____

Date	Time	Measured amount of urine	Did you have leakage, yes or no?	Approximate amount of leakage	Time you went to bed/got up, drank coffee or soda, any other comments

This diary will help us determine why you have trouble holding your urine, or why you go to the bathroom very often

FIGURE 15.4 Example of urolog. (From DuBeau CE. Treatment of urinary incontinence. http://www.uptodate.com. Updated October 2011. Accessed December 2, 2013.)

TABLE 15.6 Indications for Urodynamic Testing

- History is unclear and/or the diagnosis is uncertain.
- Invasive or surgical treatments are being considered for treatment.
- Conservative management has failed.
- Mixed stress and urge symptoms are present.
- History of prior surgery for incontinence or prolapse
- Neurologic disorders are present or suspected.

incontinence, history alone was 73% sensitive but only 55% specific.[65] For these reasons, clinicians should be aware of what diagnostic information urodynamic tests can and cannot provide, its limitations and issues, and how to accurately interpret or even studies that seek to establish their efficacy.[66]

Controversy exists with respect to the indications for urodynamic testing prior to conservative therapy for overactive bladder (OAB). From a practical standpoint, if the symptoms of urge and frequency dominate the patient history, a postvoid residual (PVR) in some instances, (discussed later) and making sure the patient

does not have a medical contraindication would seem to be all that would be necessary to initiate therapy. There are no randomized controlled trials showing prospective urodynamic testing improves treatment outcomes for either SUI or OAB.[67-69] The testing is also invasive, may be embarrassing for patients, and not cost-effective to apply as a universal policy. Experts mainly agree it is not necessary to perform urodynamic testing on patients prior to instituting conservative management.[70]

The most commonly performed urodynamic study is filling and voiding fluid cystometry, a test that is also referred to as a cystometrogram (CMG). The term is also used to indicate the graphic results of the measurements made during cystometrography. Fluid cystometry provides information on bladder proprioception (sensation) and capacity, may demonstrate the presence of detrusor overactivity (uninhibited contractions), and evaluates bladder contractility and voiding efficacy. Carbon dioxide was used in the past for cystometry, but it is unreliable because the gas is compressible, irritates the bladder, and does not allow for stress testing or any voiding studies. The use of simple office cystometry, single-channel or multichannel cystometry, ambulatory urodynamics, or videourodynamics is not necessary before starting conservative treatment for UI, or for the women with a clear clinical diagnosis of SUI; nor is it recommended for the patient who seems to have straightforward OAB symptoms.

For those patients undergoing CMG evaluation, the patient comes to the testing visit with a comfortably full bladder. Some urogynecologists advise that the patient empty her bladder and then have any PVR measured. This may be done with a bladder scan, pelvic ultrasound, or directly with a catheter. Ultrasound allows immediate measurement but is less accurate (85 to 94% accuracy) than using a catheter for PVR measurement.[71] A PVR less than 50 mL is normal when total bladder volume is 150 mL or more, whereas a PVR greater than 200 mL suggests urinary retention or poor detrusor contractility. The clinical significance of volumes between 50 and 200 mL is unclear. However, the recommendation of measuring PVR is based on opinion and is not supported by any high-quality evidence from randomized trials. The 4th International Consultation on Incontinence recommends against PVR testing as part of the initial evaluation.[60] A single PVR requires later repeat confirmation before being considered significant[37] (Table 15.7).

CMG testing is a pressure and volume recording during bladder filling. Cystometry can be done with only one channel measuring bladder pressure alone, although the information obtained with single-channel measurements may not be highly reproducible. Use of an additional channel that simultaneously measures abdominal pressure through the rectum or vagina is preferred. Use of multichannel testing can differentiate between changes in abdominal versus bladder pressure changes, that is, the increases in pressure are due to a detrusor contraction and not simply tensing of the abdominal wall. Uninhibited bladder contractions, which represent detrusor overactivity, are present in 8 to 63% of UI patients. The incidence of unstable contractions is increased by making filling CMG more provocative (e.g., faster filling speed, change in posture from supine to standing, cold-water filling, repetitive coughing, heel bouncing, hand washing). Some equipment will also allow for measurement of urethral pressure, which is discussed later in the chapter as urethral leak point pressure. The most common reason to do CMG testing is to distinguish between stress incontinence and detrusor overactivity; CMG testing may also help identify patients with mixed incontinence or abnormalities with bladder sensation.

TABLE 15.7 Patients in Whom Postvoid Residual Measurement May Be Helpful

- A recurrence of incontinence or development of a new type of incontinence after anti-incontinence surgery
- Significant pelvic organ prolapse
- Presence of specific neurologic disease (e.g., spinal cord injury, Parkinson disease)
- Failed empiric antimuscarinic drug therapy
- History of recurrent urinary tract infections
- Urodynamic testing shows detrusor underactivity or bladder outlet obstruction
- History of urinary retention
- History of severe constipation
- Use of medications known to possibly suppress detrusor contractility or increase sphincter tone
- History of diabetes mellitus with peripheral neuropathy

There are tests called "eye ball" or "poor man" office cystometrics where a catheter attached to a graduated measuring device is used to fill the bladder while observing changes in the fluid level (thought to represent changes in bladder pressure) visually through the transparent measuring device. This approach supposedly assesses detrusor activity and bladder sensation, capacity, and compliance. However, because there are no transducers to demonstrate the source of changes in pressure, it is not possible to distinguish between increased abdominal tension or a detrusor contraction. It is highly possible that use of this methodology will lead to overestimation of detrusor activity. This being the case, it would seem a poor choice to rely on the "eye ball" technique to detect these subtle differences.[37,72]

Presently, the preferred method of cystometric evaluation is called complex multichannel CMG. These studies are generally performed in a urodynamic laboratory and involve bladder filling with a specified liquid at body temperature (usually water or saline) at a selected rate. Most clinicians fill the bladder at a rate of 50 to 100 mL/minute (faster rates may provoke detrusor activity). The pressure recording system is calibrated to zero at the superior edge of the pubic symphysis. To start, the bladder is empty. Patients are placed in a sitting or semistanding rather than the supine position.

During filling CMG, several data points are obtained. These include the volume at which the patient experiences the following:

- The first sensation of bladder filling
- A desire to void but one that can be tolerated
- Urgent need to void
- Maximum capacity; patient can no longer avoid micturition

During testing, any abnormal bladder contractions—seen as increases in detrusor pressure—whether they are spontaneous or provoked are noted and are abnormal. At the end of testing, the volume infused into the bladder divided by the change in detrusor pressure is calculated to give an estimate of bladder compliance. Bladder compliance is expressed as mL per cm H_2O and can be affected by bladder filling; faster filling is more provocative. Reduced or absent bladder sensation during CMG is noted. Pain during filling CMG is abnormal, and if it occurs, its site, character, and duration is noted.

There are no recognized standards for normal values on CMG. Commonly used ranges include 100 to 200 mL at the first desire to void, a normal desire to void is often felt between 150 and 350 mL, urgency may be noted between 250 and 500 mL, and maximum cystometric capacity (when patient can no longer delay micturition) ranges between 300 and 600 mL. A small rise in detrusor pressure (i.e., less than 10 to 15 cm H_2O) without undue sensation of urgency up to a capacity of 400 to 500 is also normal. These values are reflective of wide ranges of normal, and testing with results outside these values is not conclusive for pathology per se. Correlation between symptoms, physical findings, and testing results must be done to arrive at a meaningful assessment (Table 15.8).

Detrusor activity (inherent bladder wall pressure) should change very little with bladder filling. Detrusor overactivity is the occurrence of involuntary detrusor contractions during filling CMG and is seen as wave forms on the CMG of variable duration and amplitude. Symptoms, such as urgency and/or urgency incontinence, may or may not occur. If a neurologic disease is the cause for contractions, then neurogenic detrusor overactivity is diagnosed; otherwise, idiopathic detrusor overactivity is the term used.

A stress test is performed using provocative measures during or after the CMG. Such measures may include coughing, Valsalva, heel bounce, running water, and are done to see if there is any associated loss of urine and then correlate the loss with any noted detrusor activity, that is, detrusor overactivity, or if there are no detrusor contractions associated with the loss, which would be indicative of stress incontinence. A stress test is best performed in the lithotomy or standing position, and enough fluid (200 mL) needs to be placed into the bladder before declaring a negative test result. If a slight amount of urine is lost a few seconds after the stress effort or a large amount is lost suddenly with minimal stress, this may indicate detrusor instability.

A simple office evaluation for SUI described by Videla and Wall[73] consists of four components: a predominant complaint of SUI, positive cough stress test, PVR less than 50 mL, and a functional bladder capacity greater than 400 mL determined by a voiding diary. When compared with complex multichannel urodynamic evaluation, SUI was confirmed in 72 (97%) of 74 patients. It has been shown that 25 to 30% of the women with SUI do not have urodynamic stress incontinence on urodynamic testing.[74]

Ambulatory urodynamics are investigations of the lower urinary tract, performed outside the clinical setting, involving natural filling and reproducing the woman's everyday activities. There is some data that ambulatory urodynamic testing may be more sensitive than conventional urodynamics in diagnosing detrusor overactivity.[75,76] However, they are expensive, and due to issues with data gathering, these are currently only recommended for use in clinical trials and not routine practice.[77]

TABLE 15.8 Known Issues Affecting Urodynamic Testing Results and/or Interpretation of Results or Studies

- Urodynamic testing lacks standardization of technical details such as patient position, type of pressure sensor, and filling rate; each of these variables significantly affect results.
- The setting of a urodynamic laboratory is known to nonphysiologic results in some patients.
- Use of a transurethral catheter may unmask stress incontinence in some patients.
- There may be inconsistency in the reproducibility of test results in the same patient.
- There is a wide range of physiologic values in normal, asymptomatic patients.

The absence of a specific abnormality during urodynamic testing does not conclusively show it does not exist; conversely, not all abnormalities found during urodynamic testing are clinically significant.

Urethral Function

During normal bladder filling, the intraurethral pressure should be the same or greater than the pressure inside the bladder. A low urethral pressure may be found with incontinence and is associated with multiparity, hypoestrogenism, aging, and in some cases, prior urogynecologic surgery. The urethral pressure profile (UPP) measures the intraluminal pressure along the entire length of the urethra while the bladder is at rest. Urethral pressure measurement is done by several techniques, which are inconsistent between methods and even within a single method. When measured, methodology should be noted including patient position, catheter type, transducer orientation, fluid and rate of infusion, bladder volume, and rate of catheter withdrawal. The UPP is measured to help distinguish genuine stress incontinence (GSI) from intrinsic urethral sphincter

deficiency. When obtaining the UPP, several measurements are obtained:

- Maximum urethral pressure measured
- Maximum urethral closure pressure (MUCP)—the difference between maximum urethral pressure and intravesical pressure; MUCP decreases with age and with prior surgery for incontinence in some women.
- Functional urethral length (FUL)—the length over which the urethral pressure exceeds the intravesical pressure during stress; decreases with age and with loss of estrogen
- Pressure transmission ratio (PTR)—the increment in urethral pressure on stress as a percentage of the simultaneous increment in vesical pressure; when several PTR are defined at different points along the urethra, a pressure transmission "profile" is obtained.

Patients with detrusor overactivity must be treated prior to obtaining a UPP because detrusor overactivity may decrease in FUL and PTR with bladder filling.[78]

Because the UPP is obtained with the urethra at rest, its use in obtaining a clinical diagnosis is limited. However, there are some studies that indicate that a low MUCP (usually less than 20 or less than 30 cm H_2O) may be helpful in identifying women at risk for a poor outcome with retropubic suspension surgery for incontinence.[79] Women younger than 25 years have a mean MUCP of 90 cm H_2O, whereas women older than 64 years of age have a mean of 65 cm H_2O.

Leak point pressure (LPP) refers to the amount of abdominal pressure required to overcome urethral resistance and produce urine leakage when the patient is not trying to void. The pressure may be produced by a cough or Valsalva maneuver, although the leak point with cough may differ from the leak point with Valsalva. LPP is used to assess intrinsic sphincter function and is more reliable than UPP for diagnosing intrinsic sphincter deficiency. Making this diagnosis reliably is quite useful in choosing the best invasive procedure to use, for example, a sling procedure or periurethral bulking agent in lieu of a retropubic suspension. There is no standard method for measuring LPP, and a number of variables may impact the results. Multiple estimates at a fixed bladder volume (200 to 300 mL) are desirable. LPP below 60 cm H_2O is a commonly accepted value to confirm the diagnosis of intrinsic sphincter deficiency.

Dysfunctional Voiding

Dysfunctional voiding is evaluated by uroflowmetry, which measures the volume of urine voided over time, with or without a concurrent pressure-flow study which measures detrusor pressure during voiding. Dysfunctional voiding is more common in men than women, but it may occur in women with outlet obstruction or weak detrusor activity, for example, in some neurologic conditions. The predictive value of uroflowmetry in identifying women at risk of poor outcome with urogynecologic or radical pelvic surgery is controversial.

Although there are no standard values for a normal uroflowmetry exam, generally speaking, a normal exam shows a voided volume greater than 200 mL over 15 to 30 seconds, a maximum flow rate greater than 15 mL/second, and a continuous curve of flow. Flow rates less than 15 mL/second may indicate outlet obstruction, a significant increase in intra-abdominal pressure during voiding, or detrusor weakness. If a low flow rate is noted, a pressure-flow study is indicated to determine the reason for the low flow rate. If the detrusor pressure noted during the pressure-flow study is high, that is, greater than 50 cm H_2O, a urethral obstruction such as a tumor or stricture or urethral overactivity (detrusor sphincter dyssynergia) may be present. The most common cause of obstructed voiding in women is prolapse of the anterior vaginal wall, which may lead to kinking of the urethra. Another cause is previous gynecologic surgery which may have led to bladder denervation and a weak detrusor muscle. The most common reason to obtain uroflowmetry with a pressure-flow study is for voiding dysfunction after pelvic surgery.

A low flow rate may also be due to an acontractile or weak detrusor muscle. In these cases, the patient will have little or no increase in true detrusor pressure during the pressure-flow study. Voiding occurs in these patients primarily through the use of increased abdominal pressure. True detrusor acontractility may be due to neurologic abnormalities, for example, spinal cord lesions or multiple sclerosis.

Detrusor sphincter dyssynergia (DSD) is incoordination between detrusor and sphincter during voiding secondary to a neurologic abnormality. This is a feature of neurologic voiding disorders. Videocystourethrography, a CMG with real-time video, and recording is valuable to confirm this diagnosis.[80]

Imaging

Imaging (magnetic resonance imaging [MRI], computed tomography, x-ray) is not recommended for the routine assessment of women with UI. Imaging is used to assess parameters more objectively for research purposes, but routine use of imaging has not shown improvement in outcomes.[80]

Videocystourethrography (VCU) is a radiologic test allowing direct visualization of the bladder, urethra, and UVJ through a contrast medium instilled into the bladder. Urethral mobility can be appreciated on lateral views, although bony structures may impair the quality of images. VCU has long been considered by some as the "gold standard" to investigate voiding dysfunction, although it is not recommended in clinical practice except in special circumstances because it requires special facilities and exposes patients to radiation.[80]

Management and Therapy of Urinary Incontinence

The underlying etiologies of stress and urge incontinence are quite different. Urethral sphincter weakness is the main cause of SUI and represents a structural or mechanical type of malfunction; with urge incontinence, neurourinary pathology, perhaps in combination with age-related factors, comorbid conditions, medications, and functional and cognitive impairments, seems to be the underlying mechanism. The treatments for UI are geared toward addressing these different mechanisms. Urinary urgency or OAB is defined as urinary urgency, often accompanied by frequency or nocturia, may or may not be associated with urge incontinence. It is estimated to affect about one in six American women and increases with age.[81] OAB increases the risk of falls and depression; hurrying to get to the toilet increases the risk of falls by 30% and fractures by 3%.[82,83] Due to the unpredictable nature of OAB, common coping strategies include drinking less, voiding frequently, avoiding social interaction, toilet mapping, carrying spare clothing, and avoiding long journeys, all of which can lead to social exclusion.

In contrast to treatments available for stress incontinence, which may have a long-term cure rate of higher than 80%, medical and surgical treatments for OAB achieve few long-term cures and largely show only modest improvement.[84]

Stress Urinary Incontinence Treatment Modalities

Treatment for SUI ranges from conservative and behaviorally based to surgical approaches.

Pelvic Floor Muscle Training (Unassisted)

Pelvic floor muscle training (PFMT), also known as Kegel exercises, consist of repeated contraction of the pelvic floor muscles. They are used to strengthen urethral closure mechanisms through small numbers of isometric exercises at maximal exertion. To be effective, PFMT must be performed without Valsalva or accessory muscle involvement. PFMT has been shown to be helpful for some women in all types of UI. For this reason, it is recommended as a first-line conservative therapy for women with UI. Treatment effect might be greater in younger women (age 40 to 60 years) with SUI alone, who participate in a supervised PFMT program for at least 3 months.[70]

Many women have difficulty identifying and isolating the pelvic floor muscles or find the need for daily practice burdensome. As a result, the compliance rate with this therapy ranges from 60 to 90%. PFMT is ineffective in patients with denervation injury or anatomic muscle detachments.

There are many exercise schedules for PFMT, such as squeeze and hold the pelvic floor muscles up to 10 seconds; relax 15 seconds; repeat 10 squeezes in each of the lying, sitting, and standing positions, and repeat the program three times daily. Verbal instruction alone on PFMT exercises without digital instruction on examination is inadequate, resulting in appropriate pelvic floor contraction in only 60% of patients. In patients receiving verbal instruction only, up to 25% of them substitute a counterproductive Valsalva maneuver for the proper pelvic floor contraction necessary. The provider cannot assume patients can identify the appropriate muscles unless they are directly tested during a digital vaginal examination. Patients may also be instructed weekly by an incontinence specialist. A daily maintenance program is essential to preserve the effect of therapy. PFMT may be assisted by biofeedback, such as with a vaginal probe or a set of intravaginal weights (vaginal cones).[85] Starting with the lightest cone (20 g), patients insert the cones and maintain them intravaginally for 15 minutes, twice daily, by contracting their pelvic floor muscles. When they can retain a weight without difficulty, they progress to the next higher cone (up to 100 g).

If patients fail the PFMT program or cannot perform the exercises as outlined, portable biofeedback monitors may be prescribed to assist with PFMT at home. One such biofeedback program is functional electrical stimulation (FES). This therapy uses a vaginal probe, connected to a 9-volt battery source and energy modulator. A setting of 20 to 50 Hz is used, with a cycle of 5 seconds on and 5 to 10 seconds off. FES is less effective than PFMT, but it can be useful in identifying the appropriate pelvic muscles for contraction. There is some evidence the biofeedback is no better than self-help information or verbal feedback.[86]

Neuromodulation is reported to be effective for SUI and OAB. The cure and improvement rates with pelvic floor neuromodulation in SUI and OAB are 30 and 50%, and 60 and 90%, respectively. Anal and vaginal surface electrodes are used for external, short-term stimulation and sacral nerve stimulation for internal, chronic (long-term) stimulation. The effectiveness of neuromodulation has been verified in a randomized controlled trial, but the superiority to other conservative treatments, such as PFMT, has not been confirmed.[87]

Pessaries and Intravaginal Devices

There are a few pessaries designed specifically for SUI. These include the incontinence ring and incontinence dish pessaries, the Uresta incontinence pessary, the Contiform intravaginal device, the Cook Continence Ring, the Introl bladder neck support prosthesis, and the ConTIPI disposable intravaginal device. They are designed to work by compressing the urethra against the upper posterior portion of the symphysis pubis, which causes an increase in urethral resistance that ultimately prevents leakage associated with sudden increases in abdominal pressure (i.e., cough or Valsalva). Compared to PFMT, pessaries are not as effective in the first few

months of use, but long-term use shows similar efficacy for both treatments. Pessaries improve incontinence by improving urethral function. Anatomic and functional changes seen with urodynamic studies and MRI include increases in urethral closure pressure, decreased posterior urethrovesical angle, elevation of the bladder neck, and increased urethral lengths.[88,89]

The Ambulatory Treatment for Leakage Associated with Stress Incontinence (ATLAS) randomized trial of 446 women with stress incontinence to one of three treatment groups: continence pessary, behavioral therapy (PFMT and other strategies), or combined use of a pessary and behavioral therapy.[90] At 3 months, significantly fewer women in the pessary compared to the behavioral or combined groups reported a complete absence of bothersome incontinence symptoms (pessary, 33%; behavioral, 49%; combined, 44%) and treatment satisfaction (63, 75, and 79%, respectively); outcomes did not differ significantly between the behavioral and combined groups. At 12 months, however, there were no significant differences among the pessary, behavioral, and combined groups in the proportion of women who reported an absence of incontinence symptoms (35, 40, and 33%, respectively) or patient satisfaction (50, 54, and 54%, respectively). Discontinuation rates (not due to failed pessary fitting) at 3 and 12 months were similar for the pessary and the behavioral groups.

The incontinence ring and incontinence dish pessaries are the most commonly used (Milex Products, Inc., Chicago, IL) pessaries for SUI.[91] Although the size of the vaginal introitus, vaginal length, and, if present, prolapse stage are used to guide selection of pessary type and size, pessary fitting is mostly a trial-and-error process, and several pessaries may be needed to obtain an adequate fit. Pessaries are inserted into the vagina with the dominant hand, while the nondominant hand separates the introitus and depresses the perineal body. A nonlubricated glove is used, and a small amount of lubricant is applied to the leading edge of the pessary; if too much lubricant is used, the pessary will be difficult to control. The examiner's finger should pass easily between the pessary and the vaginal wall.

The patient should be asked to strain and cough repeatedly on the examination table, ambulate in the office, heel bounce and Valsalva in the standing position, and void and strain while sitting on a toilet. These tests will help ensure the patient will be able to void at home and the pessary will not be expelled. The patient should be told that if the pessary is expelled later at home, she simply needs to return to the office with it to allow for fitting of a different size and/or style of pessary.

The incontinence ring pessary has a knob, which is placed beneath the urethra to increase urethral pressure to treat stress incontinence. The incontinence dish ring pessary has a thin diaphragm across the ring and is more rigid than the incontinence ring pessary; it may be used in women with uterine prolapse and/or cystocele, as well as incontinence. The ring pessary is inserted by folding it in half like a taco and then inserting it with the curved side up. Once inside the vagina, the ring will open up and the lower rim of the pessary should rest behind the pubic symphysis. Once placement is confirmed, the ring should be manually rotated one-quarter turn in the vagina to keep it from folding back on itself and be expelled. The ring without support pessary is good for use in younger women because they have stronger levator muscles and a more ovoid shape to the vagina; by using a ring without a diaphragm, the ring is able to more closely conform to this ovoid shape.

The Uresta pessary is bell-shaped and has a handle at its base for easy insertion and removal. The tip of it is narrow, which allows for easy passage past the vaginal introitus, and when properly placed, the wide base supports the urethra. The Cook Continence Ring pessary is a flexible ring pessary with an inflatable balloon that lies under the UVJ. When the balloon is inflated, it obstructs the urethra and precludes the passage of urine either during times of rest or physical activity. When the patient has the urge to void or a specified time interval for voiding has been reached, she deflates the balloon and then urinates. The device is available only from the manufacturer with a letter from the prescribing provider.

The ConTIPI disposable intravaginal device is made of a flexible resin core and has a soft nylon-mesh cover. It is designed to provide support to the urethra whenever abdominal pressure is transferred to the pelvic floor. The device is inserted with an applicator, similar to a tampon, and a cotton string is attached to the mesh cover for removal. In one study of 60 women with severe SUI, 85% were markedly improved with the use of this device.[92,93]

After the initial fitting of the pessary, the patient should be followed-up within 1 to 2 weeks, so that the physician can inquire about any difficulties with pessary the patient may have noticed and recheck the fit. The pessary should be removed so that the vagina can be examined for irritation, pressure sores, or allergic reaction. The pessary should be removed and cleaned every 1 to 12 weeks, depending on the presence and amount of discharge, type of pessary, and patient comfort level. It is simply washed with plain water and mild soap. Patients must be counseled that if an incontinence pessary causes discomfort, tissue erosion, or urinary obstruction, they should be seen. If the patient is willing and able, she should be taught how to remove, clean, and reinsert her pessary every 1 to 2 weeks, with follow-up in 1 to 2 months, and annually thereafter. In cases where the woman is able to remove and reinsert the pessary, the physician should check the pessary after the patient has done so to be sure that it is correctly positioned.

Pessaries may be difficult for the elderly patient to manage because of the dexterity required to manipulate

the device, and they may have to come to a provider or have a visiting nurse check and care for the pessary. In these cases, the patient should be seen 1 to 2 months after the second visit and then every 3 to 6 months thereafter for pessary cleaning and vaginal assessment by the provider. A survey of 555 clinicians using pessaries in the United Kingdom reported that 23% changed their patients' pessaries every 3 to 6 months, 67% every 6 months, and 10% every 6 to 12 months.[93]

Introl (UroMed, Needham, MA) is a silicone flexible ring that is inserted into the vagina and has two ridges that support the bladder neck on either side of the urethra. It must be fitted by a physician and is available in 16 sizes. The patient should remove and clean the device after voiding, and remove it for intercourse. Reported adverse effects include urethral and vaginal infections as well as discomfort.

Mild stress incontinence in women, particularly when induced by exercise, may be managed by using a tampon, although it should only be worn for a short duration of time. Specially designed tampons, also referred to as continence guards, are disposable tampon-shaped devices made of polyurethane foam that are placed in the vagina with an applicator. These include the Contrelle Continence Tampon and the Conveen Continence Guard.

Other disposable vaginal devices include the Activgard (Coloplast, Humlebaek, Denmark) and the Contiform (Free Spirit Unlimited Pty Ltd., Contiform Trading, Australia). The Contrelle Activgard is an arch-shaped, single-use device with two wings. It is inserted into the vagina, using an applicator, to support the bladder neck. Patients do not have to remove the Activgard in order to urinate. When saturated with water prior to use, the Activgard does not absorb the vaginal fluids, thus diminishing the risk of vaginal dryness as well as any changes in vaginal pH or microflora. It can be used for up to 16 hours per day, although it should be changed every 4 to 6 hours during menses and is intended for single use only. The Contiform is made of a nonabsorbent but flexible elastomeric material and is shaped like a hollow tampon; it has a slightly elongated end that acts to provide urethral support. It should be removed nightly for cleaning and is usually replaced every 30 to 45 days (longer if used infrequently) when it becomes evident it no longer is efficacious in supporting the urethra. Both the Contrelle Activgard and the Contiform are available in three sizes.

Urethral Devices

Urinary control pads (Miniguard, UroMed, Impress, Softpatch) prevent, rather than absorb, urine loss in women with mild to moderate SUI. They are postage stamp-sized foam pads with hydrophilic adhesive on one side that are applied against the intralabial epithelium over the urethral meatus to provide pressure around the urethral opening. It is a single-use product and is removed before voiding or simply allowed to fall off during voiding. The patch may be worn for up to 5 hours at a time and through the night. It is removed for intercourse. It should not be used in women with UTI, vaginal infections, urge incontinence, or other forms of incontinence.

The FemAssist (Insight Medical Corp., Boston, MA) and the Bard Cap Sure Continence Shields (Bard Urological Division, Covington, GA) are soft silicone suction caps that are placed externally over the urethral meatus after applying an ointment to the inner surface to create a vacuum seal to hold the cap in place and close the urethra. It does not act as a collection reservoir. When it is in place, the labia fold over it, and the device cannot be seen or felt. When the patient needs to urinate, the suction cap is easily pulled off, and the cap may then be washed with soap and water and reapplied. Side effects include irritation and UTI. The FemAssist device can be reused for up to 1 week, and although the expense of FemAssist is offset somewhat by its reusability, its efficacy is limited, and many patients discontinue use of the device because of discomfort.

The Reliance Urinary Control Insert (UroMed Corp., Norwood, MA) is a soft, small, catheterlike insert with a balloon at its proximal end. It fits inside the urethra and inflates with a small amount of air to aid retention. The balloon rests above the bladder neck, obstructing the flow of urine. The balloon can be deflated by an attached string, allowing removal of the device and voiding. The device is disposable and U.S. Food and Drug Administration (FDA) approved. Objective measurement of urine loss in a multicenter clinical study showed 92% of patients achieved an 80% decrease in urine loss, and 80% were completely dry.[94] Complications associated with the Reliance device include bacteriuria in 30% of users, gross hematuria in 24%, mucosal irritation in 9%, and migration into the bladder.[95]

The FemSoft Insert (Rochester Medical Products, Stewartville, MN) is a sterile disposable, single-use, intraurethral, narrow, silicone tube enclosed in a soft mineral oil-filled silicone sleeve with a balloon on the tip. As it is placed into the urethra, the fluid in the balloon is transferred toward the external retainer to facilitate introduction into the length of the urethra. Once the tip enters the bladder, the fluid returns to fill the balloon at the tip, forming a mechanical barrier to retain urine within the bladder. The device comes with a disposable applicator and lubricating gel, is easily removed for normal voiding, and should be removed at least every 6 hours. It is available in different sizes and lengths. In a study of the FemSoft Insert, results for 1 to 2 years of follow-up showed that 81% of women reported they never or rarely experienced incontinence while the FemSoft Insert was in place.[96] The authors concluded its efficacy was exceeded only by surgical intervention.

Urethral Bulking Agents

Urethral bulking agents are indicated for mild SUI with a nonmobile urethra and for the patient with a mobile urethra who wants to defer, or is unfit for, surgery. It is particularly useful for elderly women who have SUI without vaginal prolapse. Any coexisting bladder instability or hyperactivity should be medically treated and managed prior to having the procedure; otherwise, it is likely to fail. The following products have been approved by the FDA as injectable bulking agents: polysaccharide spheres in a hyaluronic acid gel (Deflux Q-MED AB, Uppsala, Sweden); calcium hydroxylapatite particles (CaHA) in a gel carrier (Coaptite, Bioform Medical Inc., Franksville, WI); carbon bead technology (Durasphere Injectable Bulking Agent, Carbon Medical Technologies Inc., St. Paul, MN); glutaraldehyde cross-linked bovine collagen (Contingen Bard Collagen Implant, Collagen Matrix Inc., Franklin Lakes, NJ); ethylene vinyl alcohol copolymer implant (Bard Tegress Urethral Implant and Uryx, Urethral Bulking Agent, C. R. Bard Inc., Lowell, MA); and Macroplastique (Uroplasty Inc.). With Contigen, a skin test is performed on the patient at least 4 weeks prior to the injection to determine sensitivity to the xenograft.

In an office procedure, the bulking agent chosen is injected either transurethrally through a cystoscope or periurethrally into the submucosa of the proximal urethra. It takes about 20 to 40 minutes. Patients must be taught to catheterize because this may be necessary for a few days after the procedure. It takes about 1 month for the full benefit to be apparent. Injections often need to be repeated every 6 to 18 months. About 67 to 96% of women with intrinsic sphincter deficiency treated with Contigen remained dry 1 year after injection. After 2 years, 40 to 49% of incontinent women were cured, and 67 to 83% were either cured or improved.[97]

Autologous fat injection is also used as a periurethral bulking agent, and subjective improvement is reported to be as high as 83%; however, the cure rate declines to 57% after 1 year. Patients require one to four injections (average 2.5) to achieve continence. Because of the limited clinical efficacy compared with other methods and rare but serious complications, such as fat emboli, autologous fat is rarely used for periurethral injection.

The FDA approved carbon-bead (Durasphere) injection in 1999. In a comparative randomized, multicenter, double-blinded study with collagen (Contigen), carbon-bead injection showed outcomes similar to those of collagen injection.[98]

In a multicenter, randomized, prospective trial comparing calcium hydroxylapatite (Coaptite) injection to collagen, 63.4% of patients who underwent Coaptite injection saw significantly improved continence at 1 year.[98] The majority of women require more than one injection.

Polydimethylsiloxane (Macroplastique) injection was FDA approved in 2006. A recent randomized trial showed that at 12 months after treatment, 61.5% of patients who received Macroplastique and 48% of patients who received Contigen had dry/cure rates of 36.9%, compared to 24.8% in the collagen group.[99]

The patients whose incontinence does not improve after five separate treatment sessions of periurethral bulking are considered treatment failures, and no further treatment by that method is recommended. Injection implants should not be used in patients with bladder neck or urethral strictures until such strictures have been corrected. Various local complications have been described following transurethral or periurethral collagen injection therapy, including sterile and nonsterile abscess formation and periurethral pseudocyst development. An increase in autoimmune disease has been reported in a small number of cases, and the procedure may not be appropriate for patients with certain cardiac conditions. There is some evidence that periurethral bulking agents may be no better than saline injections.[100]

Absorbance Products

The ability of absorbance products to catch and contain urine varies greatly. There are four main designs of absorbent products used for *light UI* (that contained within a small absorbent pad): disposable insert pads, disposable menstrual pads, washable pants with an integral pad, and washable inserts. It is estimated that as many as 30% of all feminine hygiene pads are purchased for mild incontinence and not menstruation. For leakage prevention, overall acceptability, and preference, disposable inserts are better than menstrual pads, which are better than washable pants with an integral pad, which are better than washable inserts.[101] There is no skin health benefit for either washable or disposable designs. Most women preferred the disposable insert. New technology in absorbent perineal products uses a superabsorbent polymer that turns the urine into a gel, eliminating the possibility of leakage or odor. These products wick the urine away from the skin, thus reducing irritation. The urine-holding capacity of the various absorbent products varies and is not standardized.

Medical Therapies for Stress Urinary Incontinence

Alpha-adrenergic Agonists

There are few pharmacologic agents for the treatment of pure SUI. Adrenergic drugs have been used but have limited effects and significant side effects. A Cochrane Review of 22 randomized trials using adrenergic drugs in women was done.[102] The results showed that an adrenergic agonist drug is only slightly more efficacious than placebo and has high-risk side effects, including some serious ones such as cardiac arrhythmias and hypertension.

Estrogen

It is possible that estrogen deficiency may be an etiologic factor in the development of UI in women. In a Cochrane Review, 33 trials were identified, which included 19,313 (1262 local administration) incontinent women.[103] The trials used varying types of estrogen, dose, treatment duration, and length of follow-up. Systemic oral estrogens resulted in worse incontinence than placebo. The result for women with a uterus on combined estrogen and progestin also showed a statistically significant worsening of incontinence. There was evidence that estrogen used locally (vaginal creams or tablets) may improve incontinence, with one to two fewer voids in 24 hours—mainly nocturnal voids—and less frequency and urgency.

Tricyclic Antidepressants

Because they have anticholinergic and alpha-adrenergic properties, tricyclic antidepressants (TCA) may be used for the treatment of SUI or OAB. Typically, imipramine is given at a dose of 10 to 25 mg, one to four times daily. In elderly patients, doses should be kept as low as possible because the risk of anticholinergic adverse effects and orthostatic hypotension may be significant.

Duloxetine

A newer form of SUI treatment is a serotonin-noradrenaline reuptake inhibitor. It stimulates pudendal motor neuron alpha-adrenergic and 5-hydroxytryptamine-2 receptors.[104] In two large, randomized controlled trials using a dose of 40 mg twice a day, participants had moderate decreases in the frequency of incontinence compared with placebo and reported an improvement in quality of life. In two reviews, however, the authors concluded that although there was an improvement in symptoms, the objective cure rates—measured with stress pad tests and 24-hour pad weights—were not significantly different between duloxetine and placebo.[105,106] Duloxetine should not be used by patients with liver disease. Nausea is a common side effect and may be tempered by starting at 20 mg twice a day and increasing to 40 mg after 2 weeks. Approximately 20% of women stop taking the drug because of side effects.

Overactive Bladder and Urge Urinary Incontinence Treatment Modalities

Therapy for OAB and urge incontinence is primarily behavioral and pharmacologic.

Bladder Retraining

The term "bladder retraining" has been applied to several scheduled voiding regimens, including timed voiding, prompted voiding, habit training, and patterned toileting. The goal of bladder retraining is to increase the time interval between voids. Before bladder re-education starts, a baseline bladder diary is obtained. The voiding diary (urolog) is used to assess baseline voiding patterns, frequency, and voided volumes. The bladder diary is also used to assess progress once the program is started. It is important that most voids occur prior to a strong urge to urinate, and the program ends for the day at bedtime. Usually, the voiding interval is increased by 15 minutes every week for 4 to 8 weeks with the patient keeping records. The goal is a 2.5- to 3-hour voiding interval. If the patient is voiding more than once an hour and still leaking urine, it may be necessary to combine medication with the bladder retraining. PFMT (Kegel exercises) are taught to control sudden voiding urges. In clinical studies, 75 to 80% of bladder retraining participants reported improvement in bladder control.[67]

Functional Electrical Stimulation/Sacromodulation

When patients have not obtained results from bladder retraining or medication, it is feasible to use a trial of FES.[107] The settings are 5 to 20 Hz, with a cycle of 5 seconds on and 5 to 10 seconds off. There is an expected response of 50% improvement.

If FES is unsuccessful, sacral neuromodulation may be an option. Sacral neuromodulation requires an implanted electrode in the sacrum and a pacing device inserted under the buttock skin. A Cochrane Review of sacral neuromodulation concluded that continuous stimulation offers benefits for carefully selected people with OAB and for those with urinary retention without structural obstruction.[108] The devices are expensive, the surgery invasive, and many people need a second operation, either because the device did not function or for complications. Questions remain about patient selection and the best way to use these devices.

Medical Therapies for Overactive Bladder and/or Urge Incontinence

Anticholinergic drugs with antimuscarinic effects may help adults with symptoms of urinary frequency, urgency, and urge incontinence largely by increasing bladder capacity and decreasing urgency, and not decreasing involuntary detrusor contractions[109] (Table 15.9). In a Cochrane Review looking at the treatment of OAB with anticholinergic medications, nine medications were included: darifenacin (Enablex), emepronium bromide, oxybutynin (Ditropan), propiverine (Detrunorm), propantheline (Pro-Banthine), tolterodine (Detrol), trospium chloride, and solifenacin (VESIcare), and a slow-release formulation of tolterodine. The analysis of showed statistically significant improvements in symptoms and modest improvement in quality of life compared to placebo.[110] Other systematic reviews have also found that these drugs are superior to placebo.[111]

TABLE 15.9 Medications Used in Overactive Bladder and Urge Incontinence

Medication	Dosage and Administration
tolterodine (Detrol)	1 mg or 2 mg tablet twice daily
tolterodine extended release	2 mg or 4 mg tablet once daily
trospium chloride (Sanctura)	20 mg twice daily
flavoxate (Urispas)	One or two 100 mg tablets 3 or 4 times a day
solifenacin (VESIcare)	5–10 mg once daily
darifenacin (Enablex)	7.5–15 mg orally once daily
oxybutynin (Ditropan) Ditropan	5 mg (1/2 to 3 tablets daily)
oxybutynin extended release (Ditropan XL)	5 mg or 10 mg daily (up to 30 mg daily)
oxybutynin syrup	5 mg/5 mL (one teaspoon 2–3 times daily)
oxybutynin transdermal patch (Oxytrol)	One 3.9 mg system applied to the skin twice weekly every 3–4 days
oxybutynin gel (Gelnique)	One sachet applied once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs. Application sites should be rotated.
propantheline (Pro-Banthine)	15 mg before meals and 30 mg at bedtime (75 mg daily)
fesoterodine (Toviaz)	4 mg or 8 mg once daily

Known side effects of these agents include dry mouth, blurred vision for near objects, tachycardia, drowsiness, decreased cognitive function, and constipation. Patients with dry mouth and constipation may unwittingly exacerbate their urgency or incontinence by increasing fluid intake to address these symptoms. Antimuscarinic agents are contraindicated in patients with gastric retention, obstructive voiding conditions, or urinary retention; narrow angle closure glaucoma and drug interactions may occur with drugs that are potent CYP3A4 inhibitors. Caution should be used when administering them to patients with liver or kidney disease, ulcerative colitis, gastroesophageal reflux, cardiac disease, or myasthenia gravis. Patients should be warned of an increased susceptibility to heat stroke due to decreased perspiration capacity. A variety of central nervous system (CNS) anticholinergic side effects have been reported with OAB medications, including hallucinations, agitation, and confusion. Although the risks of these drugs outweigh the benefits in older patients with dementia, there is evidence that for those who are on an antimuscarinic and a cholinesterase inhibitor concurrently, there may be greater functional decline than that seen in patients using cholinesterase inhibitors alone.[112] If a patient's incontinence symptoms worsen while on antimuscarinic agents, the PVR should be evaluated because unrecognized urinary retention will worsen the frequency of incontinence. Long-term clinical adherence in the use of antimuscarinic agents is poor; in one study of 29,000 women, 58 to 71% of women had stopped using them by 6 months.[113]

Reformulation of antimuscarinic (anticholinergic) agents has shown some improved tolerability and enhanced patient compliance with treatment, which has always been a problem with this class of drugs. In addition to the convenience of once-daily dosing, claims have been made, generally by manufacturer-supported research, that extended-release agents have improved their therapeutic index, striking a better balance between efficacy and tolerability. The efficacy of antimuscarinic agents increases for up to 4 weeks, so clinicians should avoid escalating the dose, or abandoning therapy, too soon. Common types of OAB medications are listed in Table 15.3.[110]

Oxybutynin

Oxybutynin has been used for more than 30 years and has direct antispasmodic effects on the bladder. It comes in immediate release (IR), extended release (ER), and transdermal patch and topical gel formulations, and the efficacy is similar among the formulations. When choosing among the formulations, differences in cost, adverse effects, and time to onset of action should be considered. Following oral administration, oxybutynin is rapidly absorbed achieving maximum concentration (Cmax) within an hour, following which plasma concentration decreases with an effective half-life of approximately 2 to 3 hours. Wide interindividual variation in pharmacokinetic parameters is evident following oral administration of oxybutynin.

From a practitioner's standpoint, oxybutynin offers several advantages. It is a generic and cheaper than the others. If the patient is begun on the immediate-release tablet at 5 mg, the pills can be split to self-titrate the dosage from one-half of one tablet to one whole tablet four times daily by mouth. The immediate-release formulation can be used on an as needed basis, such as before a long car trip, before going to a concert, etc. Extended-release formulations cannot be similarly titrated. In the frail elderly, a lower initial starting dose of 2.5 mg given two or three times a day has been recommended due to a prolongation of the elimination half-life from 2 to 3 hours to 5 hours.[114]

Titrating the dosage may help reduce systemic anticholinergic effects, which have been reported to lead to as high as an 80% discontinuation rate. Transdermal patches may decrease hepatic and GI drug metabolism, thus minimizing serum levels of the active metabolite, N-desethyloxybutynin, which is responsible for severe anticholinergic side effects. The most common side effect of oxybutynin-transdermal was pruritus and erythema at the cutaneous application site.[115] A discontinuation rate of 10% was associated with this reaction.

Tolterodine

Tolterodine (Detrol, Pharmacia & Upjohn, New York, NY) was the first agent designed specifically for OAB. It exhibits selectivity for the muscarinic receptors in the urinary tract system in contrast to those in the salivary glands, resulting theoretically in less problems with dry mouth than oxybutynin. It is probably the most commonly used OAB medication today.

Clinical trials in patients using tolterodine for OAB showed a reduction in incontinence episodes and increase in bladder capacity. In 12-month studies, tolterodine decreased voiding frequency by 20% and the number of incontinence episodes by 74%.[116]

Fesoterodine

Fesoterodine is a prodrug that is nonhepatically metabolized to 5-hydroxymethyl tolterodine, which is the active metabolite of tolterodine. It is used in the treatment of OAB.

Trospium

Trospium (Sanctura, Indevus Pharmaceuticals, Lexington, MA) is highly selective for the muscarinic receptors in the bladder, and because of this, the drug does not undergo hepatic metabolism by the cytochrome P-4S0 system. At therapeutic levels, 80% of the drug is excreted unchanged in the urine, therefore acting directly on the bladder. It is used for both OAB and urge incontinence. Theoretically, its hydrophilic design will minimize passage of the drug across the blood–brain barrier, thus reducing CNS effects.[117] It must be taken on an empty stomach.

Solifenacin and Darifenacin

Both of these drugs are more selective for the M_3 muscarinic receptor found in the bladder and GI tract; whether this increased selectivity translates into better efficacy or tolerability is not entirely clear.[118,119] Both are used for the treatment of OAB with urge incontinence, urgency, and urinary frequency.

Mirabegron (Myrbetriq)

Stimulation of beta-3 adrenoreceptors in the bladder wall facilitates bladder relaxation and is the rationale for the creation of the beta-3 receptor agonist medication, mirabegron. A relatively new drug, its efficacy has been demonstrated in randomized trials that demonstrated reduced urinary frequency and incontinence episodes for patients assigned to medication compared to placebo.[120,121] The most common side effects observed in the trials were increased blood pressure, nasopharyngitis, UTI, constipation, fatigue, tachycardia, and abdominal pain. It is not for use in patients with severe, uncontrolled hypertension.

Mixed Urinary Incontinence

Mixed urinary incontinence (MUI) is a combination of OAB and SUI that is often difficult to separate out on urodynamics, partly because of difficulty in defining criteria as to what is MUI. In clinical use, the diagnosis is based on symptoms rather than urodynamic findings. Conservative intervention with combined PFMT and bladder retraining is an ideal initial approach. If symptoms of urge incontinence are predominant, consideration should be given to the use of anticholinergic medication as first-line therapy (Table 15.10). Mixed symptoms are more common in elderly patients.[122,123]

TCA are not specifically antimuscarinics, but because of effectiveness in decreasing bladder contractility and increasing outlet resistance, TCAs are used to treat MUI. Imipramine 150 mg daily has been recommended. With its sedating effect, imipramine often improves nocturnal incontinence.

Other Forms of Urinary Incontinence

Detrusor Hyperactivity With Incomplete Contractility

Detrusor hyperactivity with incomplete contractility (DHIC) is common in the elderly. In DHIC, the bladder contracts uncontrollably, but emptying is incomplete. The patient's bladder fills more quickly because it is never completely empty. DHIC can be misdiagnosed as SUI if detrusor activity is triggered by a stress maneuver or as outlet obstruction and detrusor weakness because it shares the same symptoms. Anticholinergic therapy aggravates the retention. Therapies include double voiding, Credé maneuver, and intermittent self-catheterization in conjunction with an antispasmodic therapy.

Detrusor Underactivity

This occurs in 5 to 10% of the population and is more common in elderly adults.[124] Symptoms include UI and urinary retention. Etiologies include low estrogen, fibrosis, smooth muscle damage, peripheral neuropathy (due to diabetes mellitus, vitamin B12 deficiency, Parkinson disease, alcoholism, tabes dorsalis), and damage to the spinal detrusor efferents by disc herniation, spinal stenosis, tumor, or congenital abnormalities. Sacral nerve stimulation may be beneficial for patients with idiopathic or neurogenic underactivity. Any issues with constipation should be addressed.

Overflow Incontinence

Overflow UI occurs when detrusor pressure is low or the outlet pressure is high, causing the bladder to distend and spill small or large amounts of urine. Overflow UI usually does not occur until the residual urine is in excess of 350 mL, and at that point, it creates enough pressure in the bladder to partially overcome urethral resistance. Low

TABLE 15.10 Efficacy of Behavioral and Pharmacologic Treatments for Urge and Mixed Incontinence

Treatment	Target Population	Efficacy
Behavioral		
Pelvic floor muscle exercises	Women	Up to 80% decrease in episodes; motivated patients
Bladder retraining	Cognitively intact	≥35% decrease in UI episodes; pt perception of cure at 6 mo RR 1.69 (1.21–2.34)
Prompted voiding	Dependent; cognitively impaired	Average reduction 0.8–1.8 in UI episodes daytime; cure rare, caregiver dependent
Habit training	Voiding record available	Highly dependent on caregiver compliance
Scheduled (timed) voiding	Unable to toilet independently	30–80% decrease in daytime episodes but study quality fair
Pharmacologic		
All antimuscarinics	Unresponsive to behavioral treatment alone	WMD in daily UI episodes 0.6 (95% CI 0.4–0.8); dry mouth RR 2.56 (95% CI 2.24–2.92)
Oxybutynin	Unresponsive to behavioral treatment alone	ER: 71% mean reduction weekly UI episodes, cure rate 23%, dry mouth 30%
Tolterodine	Unresponsive to behavioral treatment alone	ER: 69% mean reduction weekly UI episodes, cure rate 17%, dry mouth 22%
Trospium	Unresponsive to behavioral treatment alone	20 mg twice a day: 59% mean reduction daily urge UI episodes (versus 44% with placebo), cure rate 21%, dry mouth 22%, constipation 10%
Darifenacin	Unresponsive to behavioral treatment alone	7.5 mg or 15 mg daily: 68 and 73%, respectively, median reduction in weekly UI episodes (versus 56% with placebo); dry mouth, 19 and 31%, respectively; constipation 14% (both doses)
Solifenacin	Unresponsive to behavioral treatment alone	5 mg or 10 mg daily: 61 and 52%, respectively, mean reduction daily UI episodes (versus 28% with placebo), dry mouth 8 and 23%, constipation 4 and 9%, respectively
Estrogens	Postmenopausal women unresponsive to behavioral treatment alone	Topical of some benefit

UI, urinary incontinence; pt, patient; RR, relative risk; WMD, weighed mean difference; CI, confidence interval; ER, extended release.

From Abrams P, Cardozo L, Khoury S, et al, eds. *Second International Consultation on Incontinence*. Plymouth, UK: Health Publication Ltd; 2002; Fonda D, DuBeau C, Harari D, et al. Incontinence in the frail elderly. In: Abrams P, Cardozo L, Khoury S, et al, eds. *Third International Consultation on Incontinence*. Plymouth, UK: Health Publication Ltd; 2005; Diokno A, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc*. 2003;78:687–695; Zinner N, Gittelman, Harris R, et al. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol*. 2004;171:2311–2315; Cardozo L, Lisec M, Millard R, et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol*. 2004;172:1919–1924; Haab F, Stewart L, Dwyer P. Darifenacin, an M3 selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *Eur Urol*. 2004;45:420–429; Cardozo L, Lose G, McClish D, et al. A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. *Acta Obstet Gynecol Scand*. 2004;83:892–897; DuBeau CE. Treatment of urinary incontinence. http://www.uptodate.com. Updated October 2011. Accessed December 2, 2013.

bladder pressures are often caused by lower motor neuron disease, and high outlet pressures occur most often from obstruction. Low pressure overflow incontinence is most common with diabetes mellitus, stroke, multiple sclerosis, pelvic trauma, extensive pelvic surgery, and spinal cord lesions. High outlet pressures in women may occur with pelvic organ prolapse, urethral stricture, or detrusor dyssynergia. Patients may note frequent or continuous dribbling; the bladder may be palpable on exam; and urodynamic studies will reflect decreased flow rates and large capacity. Treatment employs intermittent or continuous catheterization, double voiding, relaxation exercises, or sacral neuromodulation.[125]

Urethral Diverticula

Urethral diverticula in women are uncommon and usually present between the ages of 20 and 60 years. Based on hospital and surgical records, they are three times more common in Black women than White women.[117]

Most diverticula are acquired because they are only rarely found in neonates. Etiologies include urethral injury during childbirth (although they do occur in nulliparous women), surgery, and catheterization. Most urethral diverticula occur in the middle or distal portion of the posterior aspect of the urethra, they may be unilocular or multilocular, and multiple diverticula may be present. Cases may be asymptomatic. A high index of suspicion is essential for making the diagnosis because they are uncommon, and their symptoms may be similar to other more common entities. The classic presentation includes postvoid dribbling, dysuria, and dyspareunia. Other symptoms include recurrent UTIs, incontinence, urinary retention, and vaginal mass.

Urethral diverticula are usually located at the middle or distal portion on the posterior aspect of the urethra. An anterior vaginal wall mass is found on physical examination in many, but not all, patients, and the finding of such a mass does not confirm the presence of a diverticulum.

MRI is preferred for imaging because it allows better visualization of diverticula that are small or noncommunicating although it is expensive and the expertise to evaluate findings may not be readily available. MRI is also useful in detecting findings such as a solid mass within the diverticulum (which may signify malignancy). Transvaginal ultrasound may be used for diagnosing urethral diverticula

using a high-frequency probe (greater than 7 MHz) to evaluate the diverticular wall and its contents and to measure the overall size and circumference of the urethral mass. On ultrasound, a finding of a soft tissue mass within a diverticulum with flow on Doppler is suggestive of malignancy. Diverticular wall thickening may occur from inflammation or malignancy. Transvaginal ultrasound is less expensive than MRI, but if the findings are nonspecific, further evaluation with MRI may be needed. Cystourethroscopy allows direct urethral inspection and may be used to locate the diverticulum communication site, but it must be used in conjunction with MRI or ultrasound. Traditional contrast-enhanced radiography (e.g., voiding cystourethrography, retrograde double-balloon positive pressure urethrography) is no longer recommended and has been largely replaced by MRI or ultrasound.

Malignancy has been reported in 6 to 9% of patients with a urethral diverticulum and they are usually adenocarcinomas. If malignancy is suspected, surgical excision should be performed and if necessary, staging.

Women without significant symptoms may be managed with conservative measures such as digital decompression (done by applying pressure on the suburethral mass after voiding) or periodic needle aspiration. For women who have bothersome symptoms, transvaginal diverticulectomy in the operating room is the procedure of choice.

An inflamed diverticulum may be managed conservatively by either transvaginal aspiration of the purulent material or by urethral dilation with transvaginal massage to express the purulent contents of the diverticular sac, followed by a 7- to 10-day course of antibiotics. Surgical procedures to repair a diverticulum are postponed until any acute inflammation has subsided.[126,127]

Functional Incontinence

Functional incontinence occurs when a patient would otherwise be continent but, because of physical or cognitive problems or medication side effects, is unable to reach toileting facilities in time. This may occur secondary to decreased mobility due to severe arthritis, weakness (from strokes or deconditioning), contractures, or the use of physical restraints. Functional incontinence may also be caused by medications, impaired cognition (e.g., from delirium or dementia), or excessive distance of the patient from the toilet facilities. Identification of potentially reversible medical and functional conditions is important because they may contribute to morbidity beyond that of incontinence and, if reversed, the incontinence may cease.

Patients with peripheral edema from any cause often have fluid shifts at night from recumbency, resulting in nocturia. It is important to distinguish this type of incontinence from other types to appropriately manage it and to address any other coexisting forms of incontinence that may be present. It is a diagnosis of exclusion and requires complete assessment and treatment of other potential causes of incontinence.

Urethral Syndrome

Urethral syndrome, or frequency dysuria syndrome, is characterized by frequency, dysuria, and suprapubic discomfort without objective urologic findings. Urinary frequency in this syndrome occurs during the day more than during the night. Dysuria, suprapubic discomfort, difficulty in starting urination, slow stream, and a feeling of incomplete emptying of the bladder may be present. Symptoms are partially relieved by voiding. Evaluation includes negative urinalysis/urine culture and normal residual urine determination. The 24-hour voiding diary usually shows frequent daytime voiding of small amounts but minimal nighttime activity. Cystourethroscopy is normal.

Acute dysuria of less than 2 weeks' duration and associated with urine culture of less than 10^5 bacteria/mL is referred to as *acute urethral syndrome*. The recognition of this syndrome has led to the more rational evaluation and management of these women. The differential diagnosis includes unsuspected pyelonephritis, cystitis, gonococcal infection, chlamydia infection, and vaginitis. These conditions collectively are referred to as "dysuria-pyuria syndrome" because all are associated with pyuria, which is considered a more reliable index of infection than is quantitative urine culture.

Chronic urethral syndrome is defined as recurrent irritative urinary symptoms without pyuria, or less than 10^2 bacteria/mL in urine culture. Possible etiologies include hormonal imbalances, a reaction to certain foods, environmental chemicals (e.g., douches, bubble bath, soaps, contraceptive gels, condoms), hypersensitivity following UTI, and traumatic sexual intercourse. Regardless of the initial pain-causing event, the patient has both involuntary spasms and voluntary tightening of the pelvic musculature during the painful episode, which, in addition to any residual irritant or reinjury, starts a vicious cycle of worsening dysfunction of the pelvic floor musculature. Often, the original cause of the pain has healed, but the pelvic floor dysfunction persists and is worsened by patient anxiety and frustration with the condition.

When an infective etiology is suspected, doxycycline 100 mg twice daily for 10 days or azithromycin daily for 5 days (Z-Pak) is recommended. If this treatment regimen fails, the next course is amitriptyline 10 to 12.5 mg daily. The dose is increased weekly until the dose is 25 to 50 mg. Six weeks may be needed for therapeutic effect.

During symptom flare-up, interval treatment is provided with antispasmodics and urinary analgesics. Urethral dilatation and massage is an old therapy with doubtful indications but works in some patients.

Painful Bladder Syndrome or Interstitial Cystitis

Painful bladder syndrome (PBS) or interstitial cystitis (IC) is a chronic condition, more common in women (10:1 female to male ratio), characterized primarily by bladder and pelvic pain and secondarily by an increased urge to pass urine with excessive urination both day

and night. The etiology, although uncertain, is thought to be multifactorial and associated with chronic inflammation, sensory nerve upregulation, and enhanced mast cell activation. Although prevalence estimates vary, one study concluded that between 2.7 and 6.5% of American women have symptoms consistent with PBS/IC.[128] These patients require subspecialty management.[129,131]

The diagnostic criteria used by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for research purposes requires both diagnostic cystoscopy and CMG, a minimum age, duration of symptoms, degree of frequency, and nocturia (Fig. 15.5). There is controversy as to the usefulness of these criteria in clinical practice, and often, the diagnosis is one of exclusion, having eliminated infection, malignancy, and less common but identifiable problems. Some have made a distinction using the term *interstitial cystitis* when strict diagnostic criteria are met and PBS when they are not. Diagnostic tests that help rule out other diseases include urinalysis, urine culture, cystoscopy, biopsy of the bladder wall, distention of the bladder under anesthesia, and urine cytology. A particular finding at cystoscopy is that of Bunner ulceration which, if present, is an inclusion NIDDK criteria.[132] The unknown etiology and often poor response to PBS therapy results in many treatments including oral medications, intravesical or bladder instillation therapy, dietary changes, lifestyle interventions, peripheral or transcutaneous nerve stimulation, surgical interventions, and combinations of the above.

Oral PBS treatments include pentosan polysulfate (reduces bladder mucosa permeability), hydroxyzine to inhibit mast-cell degranulation, oxybutynin (anticholinergic), flavoxate (antispasmodic), steroids (anti-inflammatory), benzydamine (nonsteroidal anti-inflammatory drug [NSAID]), cimetidine (H_2-receptor antagonist), TCA (pain blocker), L-arginine (smooth muscle relaxant), and antibiotics (amoxicillin, ciprofloxacin, clindamycin, doxycycline, erythromycin, metronidazole, and rifampin).[129] There is no best medication or regimen; each medication has shown some effect.

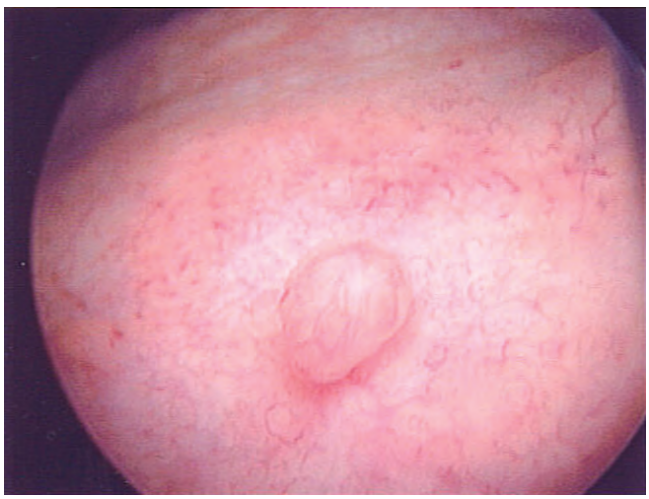


FIGURE 15.5 Cystoscopic findings in interstitial cystitis. (From Ostergard DR, Bent AK. *Urogynecology and Urodynamics: Theory and Practice*. 4th ed. Baltimore: Lippincott Williams & Wilkins; 1996:682, with permission.)

Intravesical treatments (instillations into the bladder) for PBS are commonly done, often with agents combined into what is referred to as a "bladder cocktail." These may include dimethyl sulfoxide (DMSO) (anti-inflammatory, analgesic, collagen dissolution, muscle relaxant, block histamine release), heparinoids (enhances the mucopolysaccharide/glycosaminoglycan [GAG] layer lining the bladder), pentosan polysulfate, capsaicin and resiniferatoxin (desensitization of afferent bladder innervation), bacillus Calmette-Guérin (BCG) (nonspecific immune stimulation), chondroitin sulfate (replenishment of GAG layer), disodium cromoglycate (mast cell inhibition), local anesthetics, oxybutynin, Clorpactin (tuberculosis antimicrobial), silver nitrate (antiseptic and astringent effect), and steroids.[130]

Examining intravesical therapy, Cochrane reviewers concluded that the most promising are BCG and oxybutynin. Resiniferatoxin showed no evidence of benefit but caused pain. There is little evidence to guide the use of other intravesical treatments. Adverse events were commonly reported after instillation for both active or placebo treatments. Interestingly, there was no subjective pain improvement with either Elmiron or DMSO, both commonly instilled agents. Many of the agents used may take months to show effect, making compliance less likely and their effect difficult to assess. Patients are urged to continue with therapy for at least 6 months to ensure an adequate trial to relieve symptoms.

General Health Measures and Painful Bladder Syndrome

No scientific evidence links diet to PBS, but many providers and patients feel that alcohol, tomatoes, spices, chocolate, caffeine, citrus, high-acid foods, and artificial sweeteners worsen pain. Eliminating selected dietary items and reintroducing them one at a time may determine which, if any, affect symptoms. Smoking seems to many to make their symptoms worse. How the byproducts of tobacco that are excreted in the urine affect PBS is unknown. Smoking, however, is the major known cause of bladder cancer. One of the best things smokers can do for their bladder and their overall health is to quit. Many patients feel that gentle exercise helps relieve their PBS symptoms.[131]

Bladder Retraining

People who find adequate relief from pain may be able to reduce frequency by using bladder training techniques as previously discussed.[131]

Surgery

Surgery consists of several procedures: (a) fulguration/resection of ulcers; (b) resection of scaled, ulcerated, and

inflamed sections of the bladder, leaving only the base of the bladder and healthy tissue combined with bladder reconstruction using a section of the patient's large intestine; and (c) bladder removal with reconstruction of either an autograft reservoir or stoma for external collection. Even after total bladder removal, some patients still experience pain. The decision for surgery should be made only after alternative methods fail and serious consideration has been given to potential outcomes.[131,132]

Atrophic Urethritis

Atrophic urethritis from estrogen deficiency after menopause may cause genital tract atrophy, especially the mucosal lining of the vagina and urethra. Symptoms include initiative voiding symptoms such as urgency, frequency, and pressure sensations. Estrogen administration causes engorgement within the submucosal vascular plexus and may enhance the efficiency of periurethral smooth and striated muscle. Topical treatment is initiated with a transvaginal estrogen delivery system. It takes several weeks to show an effect, and maintenance therapy needs to be lifelong. Another option to be considered is a silastic ring impregnated with estradiol (Estring) that delivers estrogen locally to the vagina, but not systemically. It releases 7.5 mcg of estradiol to the vagina daily for a period of 90 days, at which time the woman or clinician replaces it with a new ring. Efficacy of this ring is comparable to that of vaginal cream or suppositories, but it has higher rates of acceptability for some patients.

VOIDING DYSFUNCTION

Symptoms of voiding dysfunction include obstructive voiding (inability to void, voiding with high residual, altering stature or voiding position, recurrent infection), initiative symptoms (frequency, urgency, urge incontinence, infection), and nocturnal symptoms.

Obstructive Voiding

Obstructive voiding is seldom without cause; the most common are iatrogenic and follow recent surgery. A normal evaluation preoperatively followed by surgery and development of obstructive symptoms in association with a high PVR measurement makes the diagnosis. Symptomatic patients are managed by intermittent self-catheterization four to six times per day, depending on residual urine volumes and patient comfort. Antibiotic prophylaxis is usually not given because of the risk of inducing resistant organisms. Medications to improve postoperative voiding obstruction are seldom helpful, although some patients have improved with a trial of either bethanechol (cholinergic stimulant), diazepam (an alpha-blocker), or a combination of two medications. The failure of medical therapy necessitates a surgical revision of the repair.

Nocturnal Polyuria Syndrome

Nocturnal polyuria syndrome refers to a change in urine volume ratios between daytime and nighttime voiding.[133] Normally, over two-thirds of urine is excreted from 8 AM to 12 PM. Once the volume ratios change to one-half of the urine volume excreted from 12 AM to 8 AM, the diagnosis of nocturnal polyuria syndrome is made. The normal presence of the antidiuretic hormone allows one to rest comfortably overnight as concentrated urine is formed. With aging, the ability to concentrate urine declines, and daytime fluid retention and borderline cardiac function may aggravate the situation.

The urolog is the diagnostic method of choice, and both the quantity voided overnight as well as total nighttime volume is assessed. Treatment consists of fluid restriction after 6 PM, a daytime rest period especially after diuretic administration and consideration of desmopressin (DDAVP) 100 to 200 mcg 1 hour prior to bedtime. Serum sodium may drop in some patients on DDAVP, so medical status must be evaluated. If patients have nocturnal enuresis, imipramine 12.5 to 50 mg 1 hour prior to bedtime may be beneficial. Side effects must be observed carefully.

URETHRAL ABNORMALITIES

Urethral Caruncle

Urethral caruncle is an inflammatory process on the posterior aspect of the urethral meatus. It is red, may be as large as 1 to 2 cm, and can be symptomatic with bleeding and/or pain. Treatment for symptomatic caruncle is direct application of estrogen cream daily for 2 to 4 weeks. Failure to ameliorate symptoms may require local excision, laser vaporization, or cryotherapy.

Urethral Prolapse

Urethral prolapse is a protrusion of urethral mucosa circumferentially around the urethral meatus. It appears as a red ring around the urethral opening. Treatment is daily, local application of estrogen cream for 3 to 6 weeks. Excision is rarely required.

PELVIC ORGAN PROLAPSE

Pelvic organ prolapse (POP) involves the herniation of pelvic organs to or beyond the vaginal wall. Specific nomenclature is used to identify the site of herniation (Fig. 15.6).

- Herniation involving the anterior vaginal wall (cystocele) may be central, paravaginal, or a combination of both.
- Herniation within the posterior vaginal wall (rectocele) may involve the rectum, or intestinal contents (enterocele), or both.

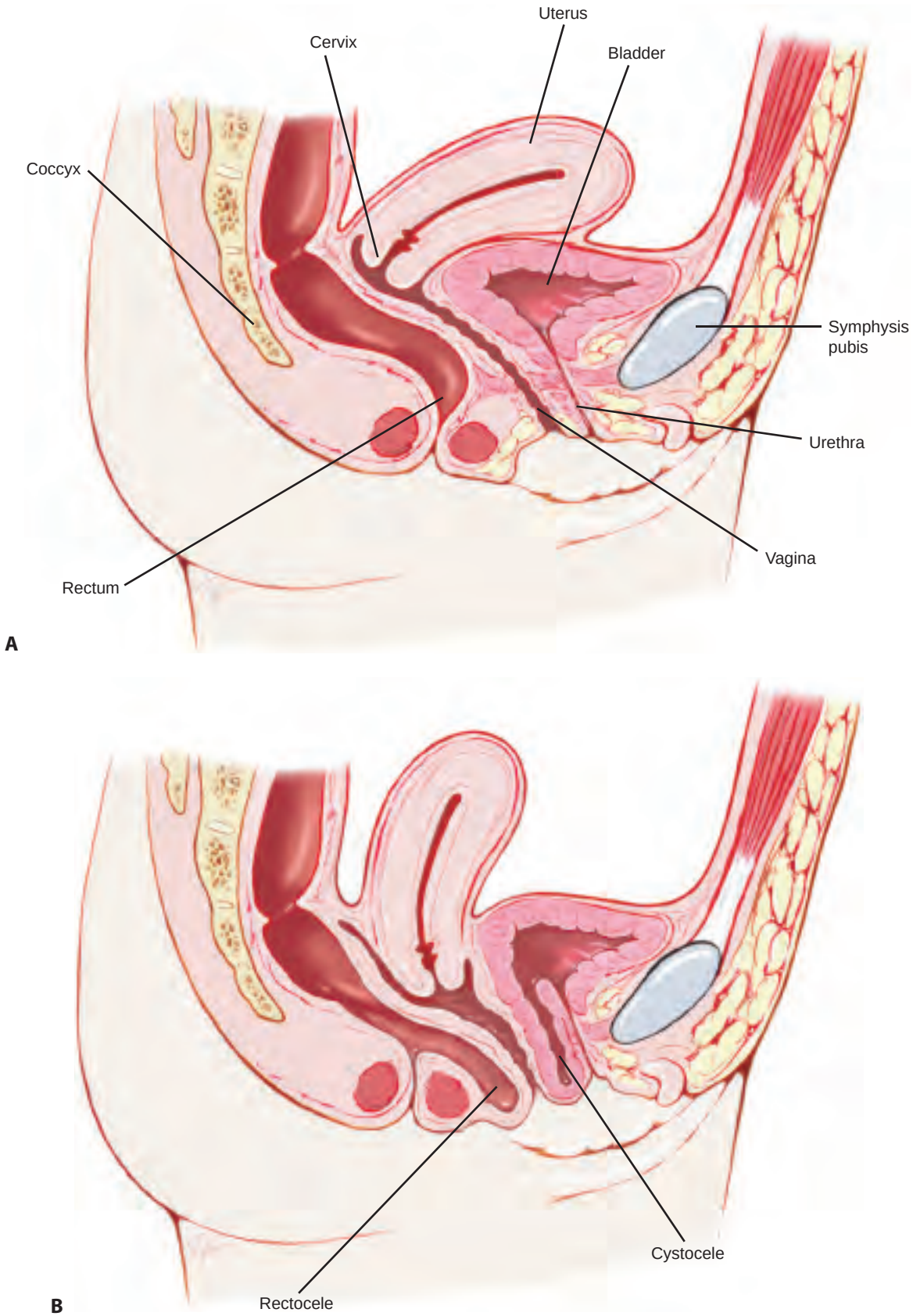


FIGURE 15.6 Examples of pelvic prolapse. **A:** Sagittal section of the pelvis showing normal anatomy. **B:** Cystocele and rectocele. (From Berek JS. *Berek and Novak's Gynecology*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.)

- Herniation of the apical component of the vagina may involve the cervix/uterus or the upper portion of the vagina or the vaginal cuff if the woman is posthysterectomy.
- Herniation of all three components is complete procidentia.

It has been estimated that in the United States, one-half of parous women have some degree of POP and 10 to 20% seek medical care. From 1979 to 2006, surgical repair of prolapse was the most common inpatient procedure performed in women older than 70 years.[134] As the population of older women grows in coming decades, the prevalence of POP is also expected to increase.

The etiology of POP is multifactorial. Risk factors include pregnancy, childbirth, congenital or acquired connective tissue abnormalities, denervation or weakness of the pelvic floor, advancing age, hysterectomy, menopause, and factors associated with chronically raised intra-abdominal pressure (obesity, chronic lung disease, constipation).

Women with POP commonly have a variety of pelvic floor symptoms, only some of which are directly related to POP. Severity of symptoms does not correlate well with the stage of prolapse. Symptoms may be related to position and may be less bothersome early in the day and become more aggravated as the day passes. Generalized symptoms of POP include pelvic heaviness, bulge/lump or protrusion coming down from the vagina, pulling sensation in the vagina, or backache. Symptoms of bladder, bowel, or sexual dysfunction are frequently present. Symptoms of SUI often coexist with mild or moderate prolapse; as the prolapse progresses, the symptoms may diminish because the prolapse is effectively "kinking" the urethra. Women may need to manually reduce the POP to assist voiding. Women with POP have an increased risk of OAB symptoms; the mechanism for this is not known.[135,136]

The most common bowel symptom associated with prolapse is constipation, but other symptoms may include fecal urgency, incontinence, or obstructive type symptoms. Defecation may be aided by pushing on the back wall of the vagina or on the perineum to evacuate stool.

POP is not associated with dyspareunia or decreased sexual desire, but women may avoid sex out of embarrassment or incontinence during sex.[137,138]

Examination and Evaluation

A site-specific physical evaluation of the pelvic floor is essential. The most common research methods for noting pelvic floor relaxation include the Baden halfway system and the Pelvic Organ Prolapse Quantification (POPQ) system. In clinical practice, it may be more expedient to use the Baden-Walker system[37] (Table 15.11).

Treatment of continent women with severe POP may unmask underlying SUI; this is especially well demonstrated with reduction at the time of urodynamics.[138]

TABLE 15.11 Baden-Walker Pelvic Prolapse Severity Guide

Grade 0—Support greater than 2 cm above the hymenal ring
Grade 1—Defect descends to within 1 cm of hymenal ring
Grade 2—Defect descends to hymenal ring
Grade 3—Defect descends 1 cm beyond hymenal ring
Grade 4—Defect extends 2 cm or more beyond hymenal ring; the uterus may be completely outside the vagina

Adapted from Scotti RJ, Flora R, Greston WM, et al. Characterizing and reporting pelvic floor defects: the revised New York classification system. *Int Urogynecol J Pelvic Floor Dysfunct*. 2000;11:48–60, with permission.

To accurately diagnose SUI in a patient with POP, one must perform a careful examination and consider urodynamic studies after reduction of any pelvic prolapse.[139]

Treatment

Treatment of POP is indicated when the prolapse is symptomatic and is associated with urinary, bowel, or sexual dysfunction. The approach to treatment depends on the associated symptoms and stage of the prolapse, the woman's general health, and provider capabilities. Options available for treatment are observation with or without exercises, mechanical with a pessary, or surgery. Women with severe prolapse who opt for expectant management should be seen on a regular basis to ensure that there is no increasing compromise to bowel or urinary function or organs.

Pelvic exercises and pessaries are the current mainstays of nonsurgical management of POP. Although routine Kegel exercises can improve pelvic floor muscle tone and GSI, evidence demonstrating improvement in POP symptoms or regression of stage is scant and inconclusive.[140,141]

Most women with symptomatic POP will have a successful pessary fitting[142,143] (Figs. 15.7 and 15.8). A short vaginal length and a wide vaginal introitus were risk factors for an unsuccessful pessary fitting. After 2 months of pessary use, 92% of women with a successful pessary fitting are satisfied. Nearly all prolapse symptoms in women resolved after 2 months; 50% of urinary symptoms improved, but occult stress incontinence may be a side effect in 23% of women.[142,143] A longer study of pessary use shows a 56% discontinuation rate at 6 years of use.[144] After cessation of use, many women may choose conservative treatment and about a third will choose surgery.

A discussion of surgical repair for POP is beyond the scope of this text.

ANORECTAL DYSFUNCTION

Anorectal dysfunction refers to a number of conditions including anal incontinence with involuntary loss of solid or liquid stool or flatus. Although there is no universal definition of fecal incontinence, most definitions imply a range of symptoms from mild to severe. It can

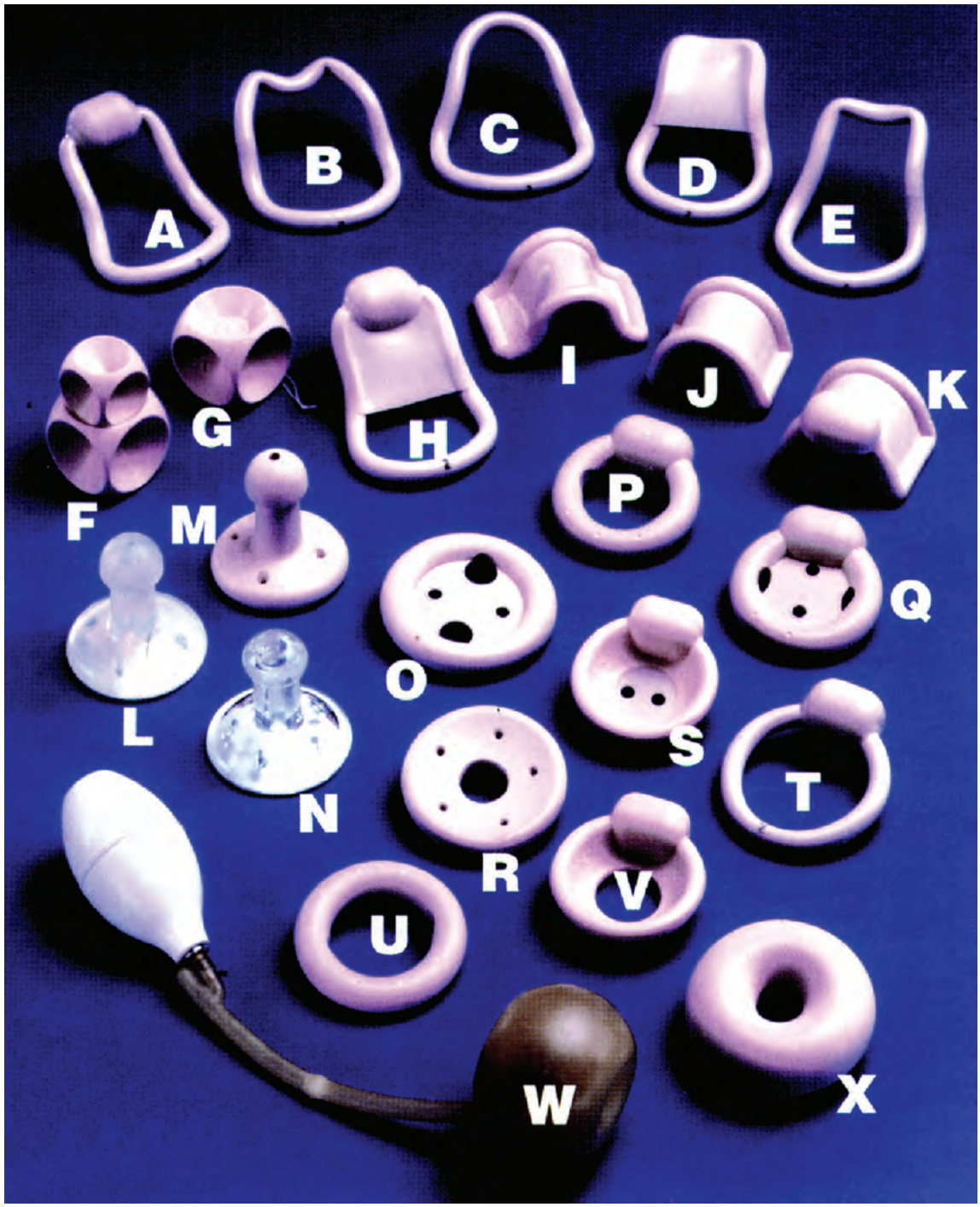


FIGURE 15.7 Commonly used pessaries. Hodge with knob *(A)*, Risser *(B)*, Smith *(C)*, Hodge with support *(D)*, Hodge *(E)*, Tandem-Cube *(F)*, Cube *(G)*, Hodge with support and knob *(H)*, Regula *(I)*, Gehrung *(J)*, Gehrung with knob *(K)*, Gellhorn 95% rigid *(L)*, Gellhorn flexible *(M)*, Gellhorn rigid *(N)*, Ring with support *(O)*, Ring with knob *(P)*, Ring with support and knob *(Q)*, Shaatz *(R)*, Incontinence dish with support *(S)*, Ring incontinence *(T)*, Ring *(U)*, Incontinence dish *(V)*, Inflatoball *(W)*, Donut *(X)*.

include passive incontinence such as soiling without sensation or warning, difficulty wiping clean, and coital fecal incontinence occurring with vaginal intercourse. It includes fecal or flatal urgency that is sudden with a compelling desire to defecate that is difficult to defer.

The inability to pass stool readily is also anorectal dysfunction and consists of straining to defecate, having to make an intensive effort (by abdominal straining or Valsalva) to either initiate, maintain, or improve defecation; incomplete (bowel) evacuation, feeling that the rectum does not empty after defecation; diminished or absent rectal sensation; constipation with infrequent and/or incomplete defecation; and frequent straining or manual assistance to defecate.

Fecal incontinence is estimated to affect 11 to 15% of community-dwelling adults and up to 47% of nursing

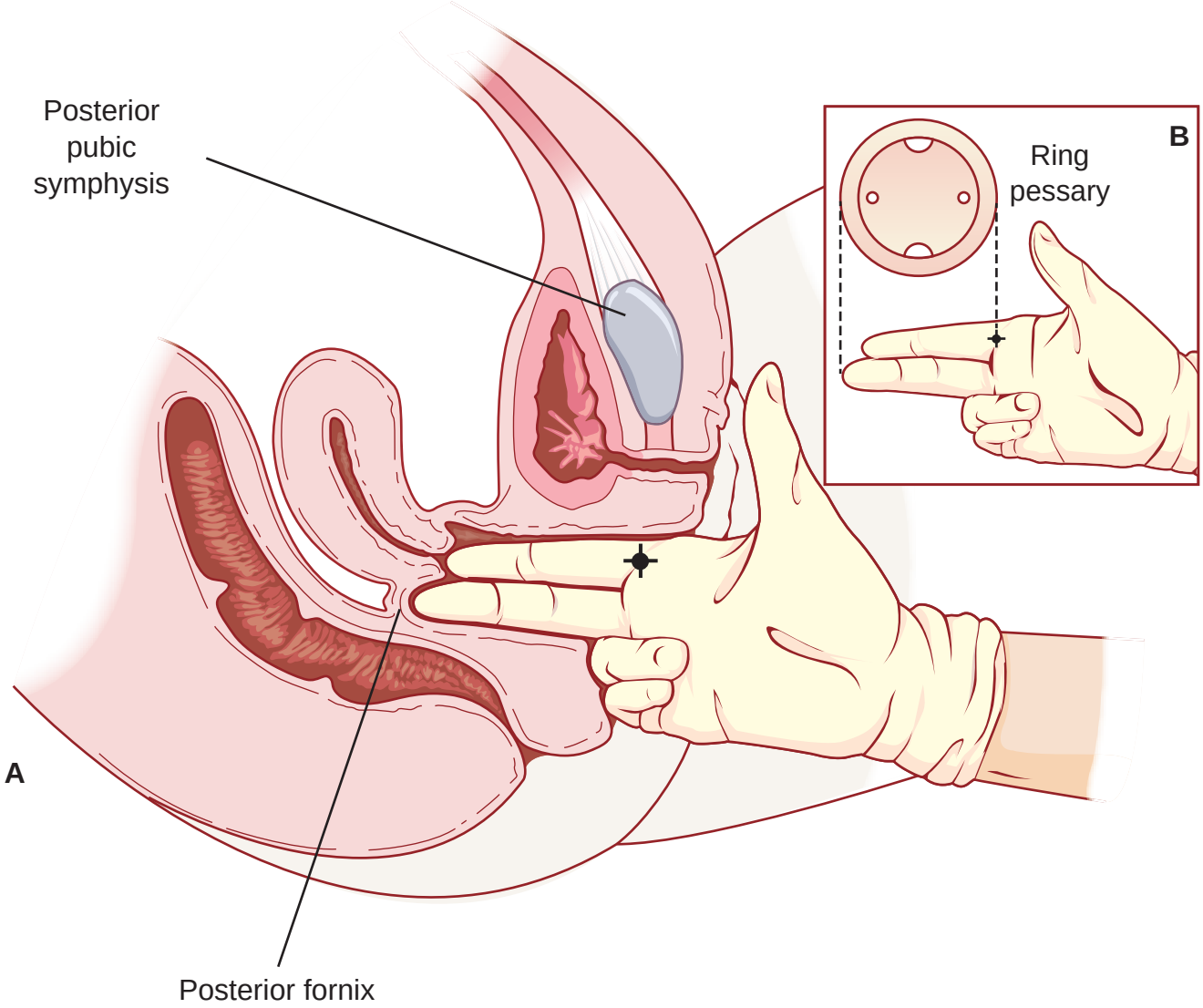


FIGURE 15.8 Estimating size of vaginal pessary required. **A:** A bimanual examination is performed to judge the distance from the posterior fornix to the posterior pubic symphysis. **B:** The spot where the pubic symphysis rests on the examining hand is mentally marked. Sample pessaries are then held up to the examining hand to estimate the proper pessary size. (Image provided by CooperSurgical, Inc., Trumbull, CT.)

home residents.[145,146] It is more common with advancing age and disability. Other associated risk factors include chronic obstructive pulmonary disease, irritable bowel syndrome (IBS), UI, colectomy, and chronic diarrhea. In women, depression and white race have been identified as risk factors; it is not clear if the prevalence is higher among women than men[147,148] (Table 15.12). Fecal incontinence may be psychologically devastating and socially isolating; many sufferers do not seek professional help, leading to further psychological impact and social isolation.

Etiologies of fecal incontinence include loose stool, rapid intestinal transit, neurologic disease or injury, obstetric or other trauma causing trauma to the anal sphincters or congenital abnormality of the anal sphincters; neurologic disease or injury causing sensory or motor impairment or decreased rectal sensation; local anorectal pathology; abnormal rectal capacitance (often seen with ulcerative proctitis or radiation proctitis), rectal retention with subsequent "overflow" leakage in frail or immobile individuals; and physical or mental disabilities impairing toilet access. Many people have combined causes for fecal incontinence.

There is some evidence that women who note altered fecal continence after vaginal delivery or who sustain fourth-degree lacerations at delivery or occult sphincter injury at delivery are at increased risk for the development of symptoms of fecal incontinence or worsening of symptoms after additional vaginal deliveries.[149,150] Consideration of cesarean section for subsequent deliveries is reasonable and should be discussed with the patient.

Nerve injury during delivery can cause incontinence many years after childbirth. Obstetric risk factors associated with nerve injury include use of forceps, a high-birth-weight infant, a long second stage of labor, and occipitoposterior presentation of the fetus.

TABLE 15.12 Causes of Fecal Incontinence

Structural abnormalities	
Anal sphincter muscles	Obstetrical injury, hemorrhoidectomy, anal dilation, radiation, inflammatory bowel disease
Rectum	Prolapse, hypersensitivity/hyposensitivity, neoplasms, congenital abnormalities, excessive perineal descent
Puborectalis muscle	Trauma, obstetrical injury
Pudendal nerve	Surgical injury, excessive perineal descent
Central nervous system, spinal cord, autonomic nervous system	Spinal cord injury, head injury, stroke, back surgery, diabetes mellitus, multiple sclerosis, tabes dorsalis, cauda equina injury or tumor
Functional abnormalities	
Anorectal sensation	Obstetrical injury, central nervous system/autonomic nervous system injury, diabetes mellitus
Fecal impaction	Dyssynergic defecation
Stool characteristics	
Volume and consistency	Inflammatory bowel disease, irritable bowel syndrome, medications, infections
Irritants	Bile salt malabsorption, laxatives
Hard stools and retention	Dyssynergic defecation, fecal impaction, medications
Other	
Physical mobility and cognitive function	Aging, disability, dementia, sedation
Psychosis	Willful soiling
Medications	Laxatives, anticholinergics, antidepressants, caffeine, muscle relaxants
Food intolerance	Lactose, fructose, sorbitol

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TABLE 15.13 Approach to Patients With Fecal Incontinence

Obtain History

Is the patient truly incontinent or does patient have frequency and urgency without incontinence?
How long have symptoms been present?
Does the patient have minor or major incontinence?
Does the patient have urgency?
Could the patient be impacted?
Is there a background history of diarrhea? Could medications be contributing?
Does the patient have a prior history of vaginal delivery or anorectal surgery?
Does the patient have a history of prior pelvic irradiation?
Does the patient have a neurologic disturbance?
Does the patient have diabetes mellitus?

Perform physical examination

Examine the external anoderm.
Test for an anal wink bilaterally.
Inspect for prolapsing hemorrhoids or other obvious pathology.
Perform a digital examination while asking the patient to bear down and to squeeze.

Obtain specific anorectal testing

Flexible sigmoidoscopy in most patients
Specific testing for patients with diarrhea
Endorectal ultrasonography in patients with suspected sphincter disruption
Anorectal manometry in patients with structurally intact sphincters

Specific treatment

Medical therapy and/or biofeedback for motivated patients who have intact sphincters and manometry showing preserved rectal sensation
Surgical repair for patients with mechanical sphincter disruption in whom medical therapy is unsuccessful
Other sphincter restoring procedures in patients with major incontinence in centers with available expertise

From Robson K, Lembo AJ. Fecal incontinence in adults. UpToDate Web site. http://www.uptodate.com/contents/fecal-incontinence-in-adults. Accessed December 2, 2013.

History

History taking should focus on patient symptoms, although directed questioning may be needed because many patients are reluctant to discuss them. The nature of the symptoms should help determine if true fecal incontinence is present or if the patient is suffering from symptoms of urgency and frequency but not incontinence. The history should include information about the onset, duration, frequency, and severity of symptoms; any precipitating events; the patient's obstetric history; any history of radiation therapy; diabetes; neurologic disease; or any prior anorectal surgery (Table 15.13).

Physical Exam

The physical examination should include close inspection of the genital and perianal areas and an internal digital examination. Perianal sensation should be tested by evoking the anocutaneous reflex (anal wink sign). This is done by lightly stroking the skin immediately surrounding the anus, which should elicit a reflexive contraction of the external anal sphincter. This should be done bilaterally. If the reflex is absent, this suggests nerve damage and interruption of the spinal arc. The digital exam is done to rule out obvious pathology and provide a crude assessment of the anal resting tone.

Anorectal Diagnostic Measurements

Although the history and exam may point toward the cause(s) of fecal incontinence in a patient, a visual assessment of the distal colon and the anus with flexible sigmoidoscopy and anoscopy is quite helpful and frequently used to exclude mucosal inflammation, tumors, or other pathology. Stool studies are indicated if there is diarrhea.

Advances in laboratory assessment techniques, such as anorectal physiology studies and endoanal ultrasound, may also allow for better identification of the underlying cause of incontinence. Diagnostic anorectal physiology measurements include resting anal pressure, pressure increase with voluntary contraction, measured duration of pressure rise on voluntary contraction, rectal sensation assessment (by balloon distention and/or electrical means), and saline retention testing. The American Gastroenterological Association (AGA) guidelines for

anorectal testing techniques or other diagnostic procedures may be found at www.gastro.org/practice/medical-position-statements. Anorectal testing may lead to changes in the diagnosis and/or treatment approach determined by history and physical alone in patients with fecal incontinence and appears to be an important part of a full evaluation.

Treatment

There are three primary treatment modalities for fecal incontinence: medical therapy, biofeedback, and surgery. The goal of medical therapy should be to reduce stool frequency and improve stool consistency. The only medications shown to be of benefit in fecal incontinence are antidiarrheal agents.[151] Loperamide seems to be more effective than diphenoxylate in reducing urgency and it also has fewer CNS side effects. Loperamide is also known to increase internal anal sphincter tone, which may improve rectal compliance. For some patients, a stool bulking agent may be helpful, although if they have decreased rectal compliance, their incontinence may actually worsen.

There is some limited evidence that use of the TCA amitriptyline at low doses can improve symptoms in patients with idiopathic fecal incontinence.[152]

Biofeedback therapy is used as a means of cognitively retraining the pelvic floor and abdominal wall musculature. Through the use of an abdominal wall electrode and electromyographic surface electrodes on an anal plug, the patient learns how to control these muscles. Biofeedback has been used for more than 30 years in the treatment of fecal incontinence, has demonstrated improvement in symptoms, and has been recommended in a guideline issued by the AGA for patients with fecal incontinence associated with structurally intact sphincter rings.[153,154] Other analyses have concluded that evidence is insufficient to assess the efficacy of biofeedback therapy for fecal incontinence.[155] It is reasonable to approach treatment conservatively first using PFMT, with or without biofeedback, and to reserve surgery as a last-resort therapy.

There are a number of surgical approaches to the treatment of fecal incontinence, ranging from direct sphincter repair to muscle replacement to colostomy in cases with incontinence refractory to other treatments or in patient who are not candidates for other therapies. In instances of a discrete sphincter tear due to obstetrical trauma, a surgical repair with anterior overlap of the external anal sphincter leads to a resolution of symptoms in approximately 80% of patients, even in those who present several years after injury, and continued continence is seen in 50 to 60% of patients 5 years after surgical repair.[156,157] Other invasive procedures include the use of neosphincters, rectally inserted balloons, injecting biomaterials into the internal sphincter (e.g., dextranomer/hyaluronic acid [Solesta] gel), silicone biomaterial (PTP, Bioplastique), and anal plugs.

Absorbent products for moderate to heavy urinary and/or fecal incontinence (typically with a total absorbent capacity of 2000 g to 3000 g) may be helpful.[158] There are four main designs of body-worn absorbent products for heavy urine or fecal loss: disposable pads (sometimes called insert pads) worn with stretch pants, disposable diapers, disposable T-shaped diapers (diapers with a waistband), and pull-ups (like toddler training pants). There are also washable versions of these. Disposable and washable underbed pads and chair pads may be used as "backup" for body-worn pads.

Women prefer disposable pull-ups, but they are expensive, and disposable inserts are a cost-effective alternative (except for women at night in nursing homes where disposable diapers are better).[158] Washable diapers are the least expensive design but are unacceptable to most women at any time. There were insufficient subjects in the trials to assess which designs are best for fecal incontinence or skin health. Using combinations of designs (different designs for day/night or for staying in/going out) may be more effective and less expensive than using one design all the time.

CONSTIPATION

Constipation is a common problem characterized by unsatisfactory defecation. It is not a single problem but has multiple presentations including hard stools, infrequent defecation (typically fewer than three per week), excessive straining with defecation, sensing incomplete evacuation, excessive time spent on the toilet or in unsuccessful defecation, and abdominal discomfort or pain. The Rome III criteria for the diagnosis of chronic constipation state that patients must experience two or more of the following symptoms for at least 3 months with symptom onset at least 6 months prior to diagnosis: (a) straining during at least 25% of defecations, (b) lumpy or hard stools in at least 25% of defecations, (c) sensation of incomplete evacuation for at least 25% of defecations, (d) sensation of anorectal obstruction blockage for at least 25% of defecations, (e) manual maneuvers to facilitate at least 25% of defecations (digital evacuation, support of the pelvic floor/perineum), and (f) fewer than three defecations per week.[159]

Additionally, loose stools are rarely present without the use of laxatives, and there are insufficient criteria for IBS. More simply, the American College of Gastroenterology (ACG) Chronic Constipation Task Force suggests the definition "unsatisfactory defecation characterized by infrequent stools, difficult stool passage or both" for constipation.[160]

Magnitude of the Problem

Difficult defecation accounts for about 20,000 hospitalizations and 2.5 million physician visits every year in the United States. Approximately 63 million North

Americans meet the Rome II criteria for constipation. Constipation is associated with medical comorbidities and significant complications, such as intestinal impaction, anal fissures, hemorrhoids, volvulus, intestinal obstruction, rectal ulcers, and IBS. Constipation can cause a significant adverse impact on patients' quality of life.

Etiology and Pathophysiology

Constipation is frequently multifactorial and can result from systemic or neurologic disorders or medications. If there is no secondary cause found, constipation may be idiopathic (primary). Little is known about the pathophysiology underlying chronic constipation. Primary constipation may be classified as normal-transit constipation (stool transit time is normal; however, evacuation is difficult), slow-transit constipation (colonic inertia; neuromuscular dysfunction), pelvic floor dysfunction (outlet obstruction, obstructed defecation, anismus, dyssynergia), or a combination of slow-transit and pelvic floor dysfunction.[161]

Evaluation

In most cases, chronic constipation may be diagnosed based on the presenting symptoms and a thorough physical examination to identify an underlying condition. A consensus guideline from the AGA recommends a complete blood count and serum glucose, thyroid-stimulating hormone, calcium, and creatinine levels. A sigmoidoscopy or colonoscopy to exclude colon cancer is indicated in patients older than age 50 years who have not had a recent examination and in those with concomitant rectal bleeding, heme-positive stool, or weight loss. When constipation does not respond to simple treatment, diagnostic testing is performed to elucidate the underlying pathophysiologic process by assessing for colonic transit time, anorectal manometry, defecography, or a balloon expulsion test.[162]

Treatment

Management of chronic constipation generally includes nonpharmacologic and pharmacologic treatments. The goal is to improve symptoms by restoring bowel function either by improving colonic transit or facilitating defecation. Conservative empiric treatment should be tried initially when no secondary cause is identified. A healthy lifestyle is recommended for the initial management of chronic constipation and laxatives used if dietary and lifestyle changes do not help.

Laxatives are the mainstay in treating constipation. The multiple types are categorized by their mode of action into bulking agents, stimulant laxatives, stool softeners, and osmotic laxatives. Two systematic reviews of laxatives for chronic constipation concluded there was good evidence supporting the use of polyethylene glycol.[160,163]

CLINICAL NOTES

- Sexually active women ages 20 to 40 years and postmenopausal women have the highest incidence of acute, uncomplicated UTI.
- The probability of cystitis in a woman with any symptom of a UTI is 50%, and if she has dysuria and frequency without any accompanying vaginal discharge or vaginitis, it is 90%.
- UTI can be accurately self-diagnosed by women 85 to 95% of the time and a short-term antibiotic regimen is highly effective curative therapy.
- Urinalysis alone is sufficient for the diagnosis of uncomplicated cystitis if the symptoms are consistent with a UTI.
- Urine culture and sensitivity testing are indicated for failed therapy or suspected antibiotic resistance, recurrent infection, suspected pyelonephritis, uncertain diagnosis after office evaluation, pregnancy, or patients at high risk for UTI.
- Approximately 70 to 90% of UTIs are caused by strains of *E. coli*. Approximately 5 to 15% of UTIs are caused by *S. saprophyticus*.
- Asymptomatic bacteriuria refers to isolation of the same organism in bacterial counts greater than or equal to 10^5 CFU/mL in two consecutive clean catch urine samples in a patient without UTI symptoms or a single positive urine specimen with greater than or equal to 10^5 CFU/mL.
- Screening for and treating asymptomatic bacteriuria should be done for pregnant women and for patients who will undergo a urologic procedure where mucosal bleeding is anticipated.
- The diagnosis of recurrent UTI is reserved for patients who experience greater than or equal to two UTIs in 6 months or greater than or equal to three within 12 months.
- Most current population-based studies of UI estimate 25 to 45% of women have UI and the incidence increases with age.
- UI is common during pregnancy and is estimated to affect 30 to 60% of pregnant women, whereas 6 to 35% of women report UI in the postpartum period.

(continues)

- A thorough history and physical examination of the woman with UI is necessary to rule out other conditions or causes as well as to identify potential causes or contributing causes of the UI.
- In general, urgency symptoms are sensitive and specific for the diagnosis of urge incontinence and a report of such symptoms is a fairly reliable diagnostic tool.
- Symptoms of slow, hesitant, or interrupted voiding patterns, straining to void, nocturia, and frequency are not diagnostically specific.
- A urinalysis should be performed for all patients complaining of UI or other symptoms.
- Asking the patient to keep a bladder diary, or urolog, may be clinically helpful. Although reliability is greatest with the use of 7-day diaries, these can be difficult to keep so it is quite common to use 2- or 3-day diaries.
- Typically, eight voids or fewer during the day are considered normal, and nocturnal frequency should be no more than two times during the night.
- There are a multitude of clinical tests measuring various properties of the lower urinary tract, also referred to as urodynamics testing, that have been developed.
- For many, urodynamic testing has become routine practice, but its role in the evaluation of incontinence for all is controversial. Experts mainly agree it is not necessary to perform urodynamic testing on patients prior to instituting conservative management.
- The most commonly performed urodynamic study is filling and voiding fluid cystometry or CMG.
- The most common reason to do CMG testing is to distinguish between stress incontinence and detrusor overactivity; CMG testing may also help identify patients with mixed incontinence or abnormalities with bladder sensation.
- Imaging (MRI, computed tomography, x-ray) is not recommended for the routine assessment of women with UI.
- Urethral sphincter weakness is the main cause of SUI and represents a structural or mechanical type of malfunction.
- Neurourinary pathology, perhaps in combination with age-related factors, comorbid conditions, medications, and functional and cognitive impairments, seems to be the underlying mechanisms of urge incontinence.
- The treatments for UI are geared toward addressing the different underlying mechanisms of the various forms of UI.
- Therapy for overactive bladder and urge incontinence is primarily behavioral and pharmacologic. Treatment for SUI ranges from conservative and behaviorally based to surgical approaches.
- Urethral syndrome, or frequency dysuria syndrome, is characterized by frequency (particularly during the day), dysuria, and suprapubic discomfort without objective urologic findings.
- If an infective etiology is suspected for urethral syndrome, doxycycline 100 mg twice daily for 10 days or azithromycin daily for 5 days (Z-Pak) is recommended.
- During symptom flare-up of urethral syndrome, interval treatment is provided with antispasmodics and urinary analgesics, and although urethral dilatation and massage is an old therapy with doubtful indications, it does work in some patients.
- PBS or IC is a chronic condition characterized primarily by bladder and pelvic pain and secondarily by an increased urge to pass urine with excessive urination both day and night whose etiology is thought to be multifactorial.
- Treatments for PBS and IC include various medications and, sometimes, intravesical treatments.
- Treatment for symptomatic urethral caruncle is direct application of estrogen cream daily for 2 to 4 weeks.
- Treatment for urethral prolapse is daily, local application of estrogen cream for 3 to 6 weeks. Excision is rarely required.
- POP involves the herniation of pelvic organs to or beyond the vaginal wall and its etiology is multifactorial.
- Treatment of POP is indicated when the prolapse is symptomatic and is associated with urinary, bowel, or sexual dysfunction.
- Pelvic exercises and pessaries are the current mainstays of nonsurgical management of POP.
- Fecal incontinence is estimated to affect 11 to 15% of community-dwelling adults and up to 47% of nursing home residents.
- In the physical evaluation of fecal incontinence, perianal sensation should be tested by evoking the anocutaneous reflex (anal wink sign) bilaterally as its absence suggests nerve damage and interruption of the spinal arc.
- There are three primary treatment modalities for fecal incontinence: medical therapy, biofeedback, and surgery.

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SECTION II

Common Nongynecologic Conditions

CHAPTER 16

Breast Disorders

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BENIGN BREAST DISEASE

Benign breast diseases encompass a heterogeneous group of lesions, which have a higher prevalence than malignant breast disease in the overall spectrum of breast disorders.[1–3] This complex group of lesions have a diverse clinical presentation from asymptomatic, nonpalpable abnormalities detected on routine breast imaging to a wide range of symptoms and clinical findings. The primary challenge for the obstetrician-gynecologist in practice is to understand the significance of these breast disorders, distinguish benign from malignant disease, identify which lesions are associated with a risk of breast cancer, and make appropriate management decisions in women where physiologic changes to the breast parenchyma can present a clinical dilemma.

CLINICAL ASSESSMENT

History

A thorough clinical assessment is the first step in the evaluation of a patient who presents with a palpable breast mass or symptoms. Key components to the initial history should include current and prior breast symptoms, duration and severity of the symptoms, menstrual history and association of symptoms in relation to the menstrual cycle, prior history of breast biopsies, and any prior imaging. Characteristics of a mass, if present, are likewise important to document because lesions that grow rapidly are more likely to be malignant, whereas lesions that change with the menstrual cycle are more likely benign. A detailed clinical assessment is listed in Table 16.1.

A breast cancer risk assessment should also be performed (Table 16.2). Age is one of the most important risk factors for breast cancer. The incidence of breast cancer increases with advancing age and is rare in women younger than the age of 40 years. Reproductive factors have also been associated with a risk of breast cancer. A longer menstrual cycle length over a woman's lifetime has been associated with a higher risk of developing breast cancer.[4,5] Nulliparous women have been shown to have an increased risk of breast cancer; in addition, a younger age at first pregnancy confers a protective effect, lowering the risk of developing breast cancer.[6,7] Alcohol consumption is also associated with increased risk of breast cancer. A standard drink contains about 10 g of alcohol, and consumption of each additional 10 g of alcohol a day is associated with a 9% increase in the risk of breast cancer.[8,9] Increased breast density on mammograms has also been identified as a risk.[10,11]

Family histories that are suggestive of an inherited predisposition to breast cancer should be considered in the initial evaluation of all patients who present with breast disease. Family history of breast cancer is a known risk factor for breast cancer, and inherited mutations such as *BRCA1* and *BRCA2* predispose patients to early-onset breast cancer.[12–15] Both inherited genes are autosomal dominant, and carriers have a lifetime risk of 35 to 85% of developing breast cancer.[14] The *BRCA1* gene mutation (chromosome 17q21) is associated with an increased risk of ovarian and prostate cancer compared to *BRCA2* mutation. The *BRCA2* gene (chromosome 13q12–13) is associated with male breast cancer, in addition to pancreatic cancer. Patients with two or more first-degree relatives with breast cancer, male family members with breast cancer, and patients who are Ashkenazi Jewish with first- or second-degree relatives with breast and ovarian cancer should be considered for genetic testing. All patients younger than 50 years of age and those with

TABLE 16.1 Key Components to the Initial Evaluation of Breast Problems

Constitutional symptoms (fever, weight loss)
Breast pain (cyclical, continuous)
Association of symptoms in relation to menstrual cycle
Presence of a breast mass (size and change)
Prior history of breast symptoms
Nipple discharge (spontaneity, color, bilaterality, number of ducts involved)
Skin changes (erythema, thickening, pain)
History of breast trauma
Previous history of breast biopsies
Prior radiologic screening
Risk factors for malignancy

the triple negative breast cancer may be tested as well. More information on *BRCA1* and *BRCA2* may be found in Chapter 21. Other less common genetic syndromes that confer elevated breast cancer risk are Cowden syndrome, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, ataxia-telangiectasia heterozygosity, and hereditary diffuse gastric cancer.[16]

The Gail risk model is a widely accepted and validated tool for individual risk assessment, which uses nonhereditary risk factors and a limited family history as part of its model.[17,18] This mathematical model uses patient's age, ethnicity, age at menarche, age at birth of first child, number of first-degree relatives with breast cancer, number of previous breast biopsies, and the presence of atypia in these biopsies to calculate the risk of developing breast cancer over a woman's lifetime.[17] The tool can be accessed online at www.cancer.gov/bcrisktool/. The Gail model may underestimate the risk of breast cancer for women with a very strong family history of breast or ovarian cancer that does not involve first-degree relatives, for example, breast cancer in the paternal lineage. The Claus model factors in a breast cancer history in up to two first- and/or second-degree maternal or paternal relatives and their ages at diagnoses.[19] The BRCAPRO model incorporates *BRCA1* and *BRCA2* mutation frequencies, cancer penetrance in mutation carriers, cancer status of the patient (affected, unaffected, or unknown), and the age of first- and second-degree relatives to estimate the likelihood of finding either a *BRCA1* or *BRCA2* mutation in a family. None of the nonhereditary risk factors is incorporated into the model, and it does not consider any other "genetic" elements involved in breast cancer; as a result, it will underestimate the risk of breast cancer in breast-cancer-only families.[20]

TABLE 16.2 Risk Assessment for Breast Cancer

Age at menarche (<12 yr)
Age at menopause (>55 yr)
Nulliparity
First pregnancy after age 35 yr
Exogenous hormone use (hormone replacement therapy)
Previous history of breast biopsies with atypical ductal/lobular hyperplasia
Alcohol consumption
Obesity
Personal history of breast cancer
Family history of breast cancer including male breast cancer
Number of first-degree relatives with breast cancer (menopausal status at diagnosis)
Family history of inherited mutations *(BRCA1, BRCA2, BART, CHEK2,* Li-Fraumeni syndrome, Cowden disease, Peutz-Jeghers syndrome)
Family history of other malignancies

From American College of Radiology. *Breast Imaging Reporting and Data System (BIRADS).* Reston, VA: American College of Radiology; 2003.

Recently, the Tyrer-Cuzick model has been developed and incorporates family history, postmenopausal hormone therapy use, benign breast disease, and a more extensive family history into its risk calculation.[21] The major advantage over the Claus model and the BRCAPRO model is that the Tyrer-Cuzick model allows for the presence of multiple genes of differing penetrance. In one study, the Tyrer-Cuzick model performed the best at breast cancer risk estimation.[22] Use of these risk assessment models in the initial evaluation of women who present with symptoms can help clinicians identify high-risk women.

The missed diagnosis of breast cancer is one of the most frequent causes of malpractice claims in the United States.[23–25] The most common situation of a missed diagnosis involves a woman presenting with a breast complaint in whom the diagnosis of cancer was delayed because of a negative clinical examination and/or mammogram.[23,26,27] Only about 50% of breast cancers occur in women with identifiable risk factors other than age so it is important to evaluate every breast complaint thoroughly.[28]

Physical Examination

As part of the initial history in a premenopausal woman, a thorough evaluation of the menstrual history including regularity, pain with cycles, and the date of the last menstrual cycle is essential prior to starting the breast examination. The breast examination is best done 7 to 9 days after the menstrual cycle has started because this is at the nadir of hormonal stimulation. The timing of the exam is not important in menopausal women or women taking hormonal treatments that cause ovarian suppression, for example, oral contraceptives.

The technique of breast examination should include inspection and palpation of the entire breast and lymph node basins (Fig. 16.1). Breasts should be inspected initially with the patient sitting in an upright position with hands relaxed by her sides. Both breasts should be compared for size, symmetry, contour, and any skin changes. Many women have a small size discrepancy between both breasts. However, any recent change in the size of the breast should be further evaluated. Previous surgical biopsies can change the contour of the breast and should be noted on examination. Edema or peau d'orange which occurs as a result of obstruction of the

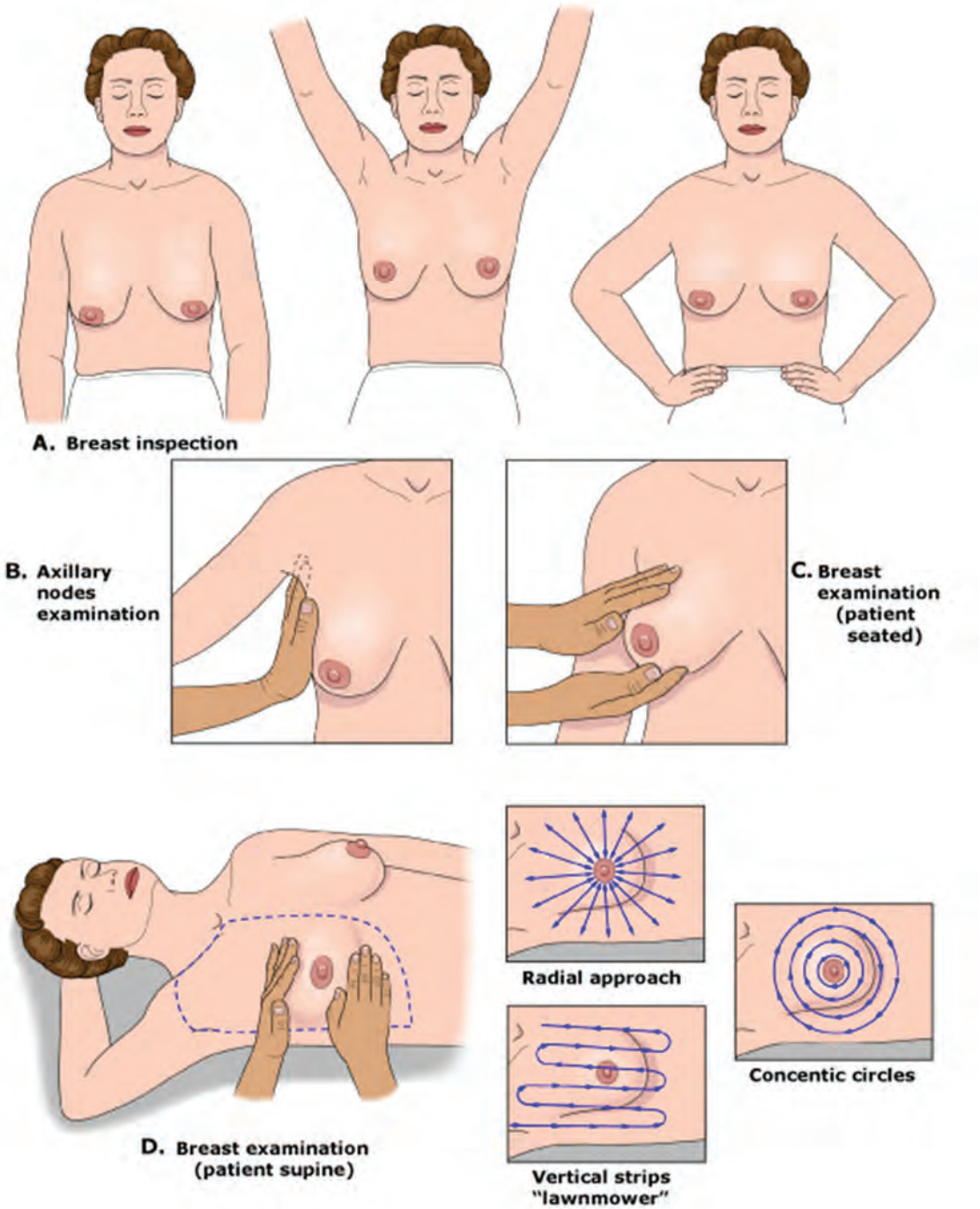


FIGURE 16.1 Clinical breast examination. **A:** The breast exam is started with the patient in a seated position with her arms relaxed. Breast inspection is aided by patient positioning. The patient is asked to raise her arms over her head so the lower part of the breasts can be inspected for asymmetry, skin changes, and nipple inversion or retraction. The patient then puts her hands on her hips and presses in to contract the pectoral muscles so that any other areas of retraction can be visualized. **B:** The regional lymph node exam is completed while the patient is still in the sitting position and includes the cervical, supraclavicular, infraclavicular, and axillary nodal basins. **C:** A bimanual examination of the breasts can be performed while the patient is still in the sitting position. This is especially useful for women with large pendulous breasts. **D:** The breast exam is completed with the patient in a supine position with the ipsilateral arm raised above her head. The area examined should extend from the clavicle superiorly to the rib cage inferiorly and from the sternum medially to the midaxillary line laterally. A systematic approach ensures that the entire breast is examined. This can be accomplished with either concentric circles, a radical approach, or vertical strips, referred to as the "lawnmower" method. (From Sabel MS. Breast masses and other common breast problems. UpToDate Web site. http://www.uptodate.com/contents/breast-masses-and-other-common-breast-problems. Accessed December 2, 2013.)

dermal lymphatics by tumor can be easily visualized. In addition, local erythema of the breast which can be caused by cellulitis, mastitis, or an abscess can be differentiated from inflammatory breast cancer, which usually presents as diffuse erythema and edema of the breast. However, diagnosis will require biopsy for inflammatory breast cancer.

The nipple areola complex should be examined for changes in the skin, symmetry, and retraction. New-onset nipple retraction should be considered suspicious for malignancy. Ulceration or eczematoid lesions of the nipple areola complex can be a sign of Paget disease.

The patient should raise her arms over her head and then place her hands against her hips, resulting in contraction of the pectoralis muscles, which can demonstrate subtle nipple retraction and dimpling of the breast skin. With the patient still in the upright position, the regional lymph node basins, including cervical, supraclavicular, and axillary lymph nodes should be examined. Palpable lymph nodes should be characterized by their size, whether they are firm, mobile or fixed, or tender to palpation. Each breast should then be palpated by placing one hand under the breast supporting it, while using the flat portion of the other hand to examine the entire breast.

The patient is then placed in the supine position, and the ipsilateral arm is raised above the head. For patients with large pendulous breasts, a towel or pillow can be placed beneath the ipsilateral shoulder to elevate the breast that is being examined. The breast should be examined either in a concentric circle or in a radial pattern, and palpation should extend from the clavicle superiorly, laterally to the latissimus dorsi muscle (posterior axillary line), inferiorly to the costal margin, and medially to the sternum. This is performed with one hand placed on the breast to stabilize the breast, while the flat surface of the other hand is used to examine the breast. Palpation of the breast should include temperature differences of the surface of the skin, edema, focal or generalized tenderness, the presence of a dominant mass, and nipple discharge. Diffuse nodularity predominantly in the upper outer quadrants of the breast is a normal finding especially in premenopausal women. Comparing physical findings of both breasts is helpful in further differentiating nodularity or other areas of palpable concern. If there is an area of nodular breast tissue in a premenopausal woman that is nonspecific, the patient may be asked to return at a different time in her menstrual cycle for a physical examination. A dominant breast mass should be different from the surrounding breast tissue on examination. If a breast mass is noted, the size (in centimeters), location, and characteristics including tenderness, mobility, and firmness should be documented. It is helpful to record the location of any abnormality on the breast by documenting its position and the distance in centimeters from the areola because this will help on subsequent follow-up examinations by either the initial physician or other examiners. Diagrammatic depictions are quite useful, and many electronic medical records do have mechanisms for the creation of such figures. In addition, if a patient reports a palpable mass that is not found on physical examination, it is important to have the patient indicate the area of the palpable abnormality noted on breast self-examination. Physical examination alone will not distinguish between benign and cancerous lesions so any abnormal findings on examination should be further evaluated using imaging, for example, ultrasound or mammography, and if necessary, biopsy.

BREAST IMAGING

Mammography

Mammography uses low-dose radiation (0.3 rad/study) and is an effective screening tool for early detection of breast cancer. It is usually the first diagnostic test ordered in women older than the age of 30 years with a new breast complaint. Digital mammography is now widely used for both screening and diagnostic studies. In contrast to film mammography where the energy from the image receptors are captured on film, digital imaging uses a digital detector that is between the breast and the compression plate to convert the x-ray images electronically and project the images onto a monitor, allowing radiologists to manipulate and enhance the images seen.

In a study by Kerlikowske et al.,[29] over 329,261 women between the age of 40 and 79 years underwent routine screening mammography. Two-thirds of the patients (638,252) had film mammography, and the remaining one-third of patients (231,034) had digital screening. Although the overall cancer detection rates were similar for digital and film mammography, the sensitivity and specificity of digital mammography was higher than film screening mammography in pre- and perimenopausal women (87.1 % versus 81.7%, respectively), women with extremely dense breasts (83.6% versus 68.1%, respectively), and women with estrogen-negative breast cancers (78.5% versus 65.8%, respectively).

Screening mammography is used to detect breast cancer in asymptomatic women, whereas diagnostic mammography is used to evaluate patients who present with clinical findings or an abnormal finding on a screening mammogram. Even if a woman has had a recent negative screening mammogram, if there is a focal complaint or change noted on exam, a diagnostic mammogram should be obtained. For screening mammography, two views of the breast are obtained: the craniocaudal (CC) and the mediolateral oblique (MLO). The MLO view is the most effective view because it includes the whole breast including the upper outer quadrant and the axillary tail. The CC view, which is performed using greater compression of the breast, provides better visualization of the medial aspect of the breast with better image detail. In addition to the MLO and the CC view, diagnostic mammograms use a 90-degree lateral view to

triangulate the exact location of the abnormality and spot compression views over the area of interest which allow for greater compression, displacing the overlying breast tissue that could obscure a lesion.

The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) uses standardized terminology to facilitate uniformity in mammography reports and includes an overall assessment of the probability of malignancy based on radiologic findings.[30] There are six categories, each associated with a specific recommendation for management (Table 16.3).

Masses and calcifications are the most common abnormalities identified on mammography. In the final reporting of these findings, radiologists should indicate the likelihood of these findings being suspicious for malignancy. These findings should be detected on both the CC and the MLO view. Irregular or lobular-shaped lesions with indistinct or obscure margins are more likely to be associated with malignancy, and round, circumscribed lesions with well-defined margins are more likely to be benign findings.

Other findings on mammography that may be associated with a mass include nipple retraction, skin retraction, and skin thickening. Focal skin thickening can be associated with benign diseases such as mastitis or malignancy including inflammatory breast cancer. Architectural distortion is seen as an area of spiculation or retraction with distortion of normal landmarks, and unless this finding is associated with a prior biopsy site, a tissue diagnosis may be required to rule out malignancy.

Calcifications in the breast as small as 50 μm can be visible on mammography. Diffuse, scattered, coarse, large, and round calcifications are almost always benign.

TABLE 16.3 The American College of Radiology Breast Imaging Reporting and Data System

Category	Assessment	Follow-Up Recommendations
1	Negative	Routine annual screening mammography (for women over age 40)
2	Benign Finding(s)	Routine annual screening mammography (for women over age 40)
3	Probably Benign Finding – Initial Short-Interval Follow-Up Suggested	Initial short-term follow-up (usually 6-month) examination
4	Suspicious Abnormality – Biopsy Should Be Considered	Usually requires biopsy
5	Highly Suggestive of Malignancy – Appropriate Action Should Be Taken	Requires biopsy or surgical treatment
6	Known Biopsy-Proven Malignancy – Appropriate Action Should Be Taken	Category reserved for lesions identified on imaging study with biopsy proof of malignancy prior to definitive therapy

Pleomorphic, heterogeneous, fine, linear, and branching calcifications have a higher probability of being malignant.[31-33] Microcalcifications associated with a mass are highly suggestive of a malignant lesion.[34,35]

Mammography should be performed prior to any planned biopsy of a palpable mass in order to better define the palpable abnormality, and to evaluate the ipsilateral and contralateral breast for additional lesions. In addition, biopsies should be performed if there is a palpable mass, despite the absence of findings on mammography. Mammography has been reported to have an overall sensitivity of 50 to 90%.[36-38] Young women who have more fibroglandular tissue or older women taking hormone replacement therapy who have extremely dense breasts will have lower sensitivity of mammography.[39-41] Murphy et al.[42] reported their experience of 1365 women with symptomatic breast cancer over a 10-year study period. They reported a false-negative rate of 10% in their study population, and these patients were more likely to be younger, have smaller tumors, and have tumors located outside the upper outer quadrant of the breast. A normal mammogram does not obviate the need for further evaluation of a suspicious mass. Mammography misses 10 to 20% of clinically palpable breast cancers.[43] If a suspicious mass is found on examination, a negative mammogram does not represent a stopping point in the workup and evaluation.

Ultrasonography

Breast ultrasonography plays an important role in the evaluation of patients with breast diseases. Focused high frequency transducers provide reliable information using noninvasive techniques.[44] It is an important adjunct to other imaging modalities such as mammography and magnetic resonance imaging (MRI). The benefit of routine screening ultrasonography has not been established; however, its role as a screening modality adjunct in women with dense breasts has been studied.[45,46] In a clinical trial by the American College of Radiology Imaging Network, 2809 high-risk women older than the age of 25 years with extremely dense breasts had screening ultrasounds in conjunction with mammography.[47] This study demonstrated that the addition of ultrasound was significantly associated with a higher likelihood of diagnosing breast cancer (11.8 per 1000 women) when compared to mammography alone (7.6 per 1000); however, the positive predictive value was low. Only 20 (8.6%) of the 233 women who were recommended to undergo a biopsy were diagnosed with breast cancer with over 90% of patients having benign findings. Other studies confer similar false-positive rates with the use of ultrasound and mammography in women with radiographically dense breasts.[48-50] The improved diagnostic yield in this population of women should be weighed against the anxiety women face from high false-positive rates and unnecessary biopsies.

Ultrasound does have reliable criteria that can help distinguish a benign cyst from a malignant solid mass.[51,52] If a lesion seen on ultrasound is a simple cyst, then no further imaging or intervention is needed. Lesions that are solid and irregular and have ill-defined margins are more likely to be malignant, and a core needle biopsy (CNB) should be performed.

The American College of Radiology (ACR) criteria for breast ultrasonography in the management of women with breast disease includes evaluation of a palpable mass or other breast-related symptoms, evaluation of lesions seen on other imaging modalities such as mammography and MRI, imaging of women younger than age 30 years or women who are lactating or pregnant, implant leaks, obscure mammographic findings in women with dense breasts, and for guidance for interventional procedures.

Magnetic Resonance Imaging

MRI provides both high spatial and temporal resolution to provide three-dimensional imaging that differentiates benign versus malignant lesions. Breast MRI has the advantage of being highly sensitive, with the ability to detect cancers that are not visualized on mammography or ultrasonography without the use of ionizing radiation.[53–55] The main disadvantages include its low specificity, high cost, and prolonged imaging time (45 minutes). Although gadolinium contrast enhancement kinetics is used to differentiate benign from malignant enhancement, benign lesions may also demonstrate contrast enhancement similar to enhancement of malignant lesions, leading to unnecessary biopsies.[56–58] A baseline blood urea nitrogen (BUN) and creatinine should be checked prior to the use of gadolinium dye because it may cause serious reactions in patients with underlying renal disease (e.g., nephrogenic systemic fibrosis and worsening renal failure).

Several large studies have demonstrated that patients most likely to benefit from breast MRI are women with breast cancer and women who are at high risk of developing breast cancer. Lesions seen with MRI may not be apparent on other imaging modalities.[59] In women newly diagnosed with breast cancer, MRI identifies additional ipsilateral disease in patients with presumed unifocal disease. This is most often observed in premenopausal women, women with dense breasts on mammography, patients with larger lesions (greater than 5 cm), those with a family history of breast cancer, and women diagnosed with invasive lobular carcinoma.[60–62] The controversy remains whether all women with a new diagnosis of breast cancer should undergo preoperative MRI given the cost. In addition, several retrospective nonrandomized trials have shown no significant differences in overall survival or disease-free survival in women with breast cancer who underwent preoperative MRI when compared to a group that did not have a staging MRI prior to breast-conserving surgery.[63–65]

MRI can be a useful clinical tool in the management of occult primary breast cancer patients who have malignant axillary adenopathy with a normal breast exam, mammogram, and ultrasound.[66,67] In addition, MRI is the most accurate imaging tool available to monitor the response to chemotherapy in patients undergoing neoadjuvant chemotherapy.[68,69] The role for MRI as routine surveillance in women with a personal history of breast cancer remains unknown; however, MRI can be useful to differentiate surgical changes versus recurrent disease in women who have undergone breast conserving surgery and have indeterminate mammographic findings at the lumpectomy site.

The American Cancer Society has recommended guidelines for MRI in addition to screening mammography in high-risk women. These categories include women who have a 20 to 25% or greater lifetime risk of developing breast cancer as determined by risk assessment tools, women with a known genetic mutation, women who have not been tested but have a known genetic mutation in the family, and women who have previously received chest wall radiation.[70]

Thermography

Breast thermography has been proposed as a method of distinguishing benign and malignant lesions and as a potential screening tool in high-risk women. Temperature maps of the breast are created using various devices that measure the heat patterns and number of vessels between both breasts, the temperature of both the skin surface and the vasculature, and the dynamic changes in breast temperature over time. Variations in the production of heat by the breast have been proposed to indicate breast disease.[71,72] There are multiple small trials evaluating the metabolic activity of malignant and benign breast lesions; however, the potential benefits as a screening tool in the detection of cancer is unknown and at this time should not be performed. In addition, the National Institutes of Health (NIH) has reported as a consensus statement that there is no data on the efficacy of thermography, and it should not be used as a screening technique for women.

DIAGNOSTIC TECHNIQUES

All suspicious lesions on clinical breast exam or nonpalpable abnormalities detected on imaging requires appropriate diagnostic evaluation using needle biopsy, either fine needle aspiration, or preferably CNB, or less commonly, surgical excision with preoperative needle localization. Excision should be reserved only for lesions not amenable to image-guided core biopsy. Figure 16.2 presents an algorithm for the management of a breast mass.

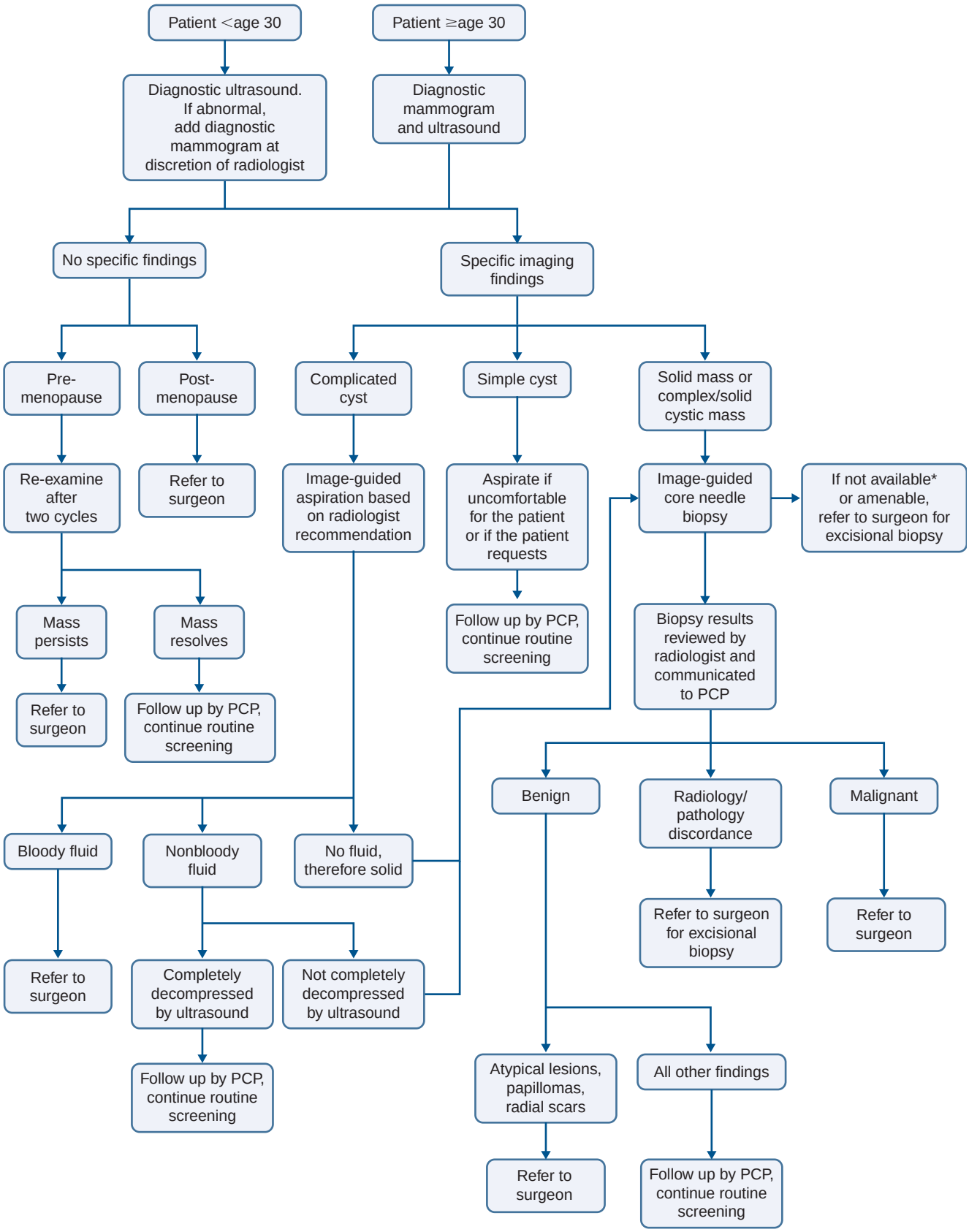


FIGURE 16.2 Algorithm for the management of a breast mass. PCP, primary care provider.

Fine Needle Aspiration

Fine needle aspiration (FNA) requires the use of a handheld syringe to percutaneously aspirate cells for cytologic evaluation. In multiple large studies, the sensitivity has varied from 65 to 91% and specificity from 46 to 100%.[73-75] Although FNA is better tolerated than CNB and enables a pathologist to immediately ascertain the adequacy of the sample, it requires a skilled cytopathologist to interpret the results. In addition, FNA is subject to sampling error because lesions are aspirated with a small 20- or 22-gauge needle, and even if adequate sampling is obtained, cytology cannot differentiate in situ or invasive carcinoma. The diagnosis is described in five categories: (a) benign with no evidence of atypia or malignancy, (b) atypia/indeterminate (nondiagnostic cellular material), (c) suspicious for malignancy, (d) malignant, (e) material is unsatisfactory for evaluation. The combination of cytology, clinical breast exam, and imaging must be correlated to achieve triple test concordance.[76] A negative FNA in the presence of findings of a suspicious mass on clinical breast exam or imaging should prompt further investigation. For patients with a diagnosis of "suspicious" or "probably malignant," a CNB or excision should be performed before definitive surgical treatment to rule out a false-positive diagnosis.[77] FNA has now largely been replaced by CNB.

Core Needle Biopsy

Over 1.4 million breast biopsy procedures are performed each year in the United States; however, a significant portion of these are performed for benign disease.[78] CNBs for palpable lesions or the use of image guidance for nonpalpable lesions is the diagnostic procedure of choice and has virtually eliminated open surgical biopsy and FNA. Image guidance can be performed using ultrasound or mammography. CNB is minimally invasive and cost-effective compared to surgical excision for diagnostic purposes. Stereotactic biopsies are performed for suspicious calcifications or density seen only on mammography and not ultrasonography. Core biopsies are associated with more discomfort than FNA but provide better tissue sampling and the ability to classify subtypes of cancer. Most procedures are being performed with either 10-, 11-, or 14-gauge devices. Vacuum-assisted devices can also be used to provide large cores enabling a more extensive sample.[79-81]

One of the challenges of CNB is the accuracy of distinguishing certain histopathologic entities. Some studies have demonstrated an inability to distinguish atypical hyperplasia from low-grade ductal carcinoma in situ (DCIS). The findings of atypia or a papillary lesion such as a papilloma warrants excision with upstaging to carcinoma seen in 4 to 20% of patients.[82-84] In addition, other investigators have demonstrated pathologic upstaging of benign papillary lesions on CNB to atypical ductal hyperplasia or carcinoma on final surgical excision.[85-87]

Incisional/Excisional Biopsy

Incisional biopsy refers to surgical excision of a portion of the lesion, whereas excisional biopsy results in surgical removal of the entire lesion. Incisional biopsies used to be the procedure of choice for diagnosing large palpable lesions; however, CNB has virtually eliminated the need for this procedure.

Excisional biopsy is only used when image-guided CNB is technically not feasible, if CNB results are discordant with clinical findings, if FNA or CNB is nondiagnostic, or if a CNB demonstrates atypical ductal/lobular hyperplasia or a papilloma.

Breast Ductoscopy/Cytology

Ductal lavage was developed as a method of collecting ductal epithelial cells from samples obtained through cannulating a duct with a microcatheter, inserting small amounts of saline, and through gentle suction, nipple aspirate is performed for cytologic evaluation. The procedure was designed to detect abnormal epithelial cells in high-risk women who had normal clinical breast exams and imaging. Ductal lavage has the ability to detect abnormal intraductal epithelial cells; however, the information gained from these results in women who have no findings on breast exam or imaging is less clear. It is not being used as a diagnostic clinical tool at the present time but is being performed in research protocols.

BENIGN BREAST CONDITIONS

Benign breast lesions are the most common presenting breast disorder seen by clinicians. Patients with benign lesions are often managed to exclude breast cancer rather than a necessity to understand and manage each of these entities.

Fibrocystic Change

Fibrocystic changes, also known as fibrocystic disease, is the most common lesion in the breast and accounts for nearly 20 to 25% of all breast lesions. Pathologists describe this entity as fibrosis with apocrine cysts and epithelial hyperplasia. Histologic findings are now classified into one of three categories that are strictly defined and correlate with the risk of developing breast cancer: nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasias. Cysts can range in size from 1 mm to several centimeters and arise as a result of individual acini or ducts that dilate and unfold and enlarge as a cyst. Haagensen[89] first described the coalescing of clusters of cysts to form a gross cyst that was palpable. Estrogen seems to play a role in producing symptoms because this entity most commonly occurs between the

age of 35 and 50 years and is extremely unusual in postmenopausal women not on estrogen replacement.

Clinical Findings

Fibrocystic changes usually produce a tender mass that is smooth, mobile, and compressible. Pain is the most common symptom and is usually associated with the menstrual cycle when cysts are known to enlarge from hormonal stimulation. In addition, fluctuations in size are often noted at various times in the menstrual cycle. Cysts can occur in multiple areas within the same breast and bilaterally with cyclical breast pain. Quite commonly, cyclical breast pain is focal without the detection of cysts on imaging or physical examination, and no cause can be identified.

Diagnostic Tests

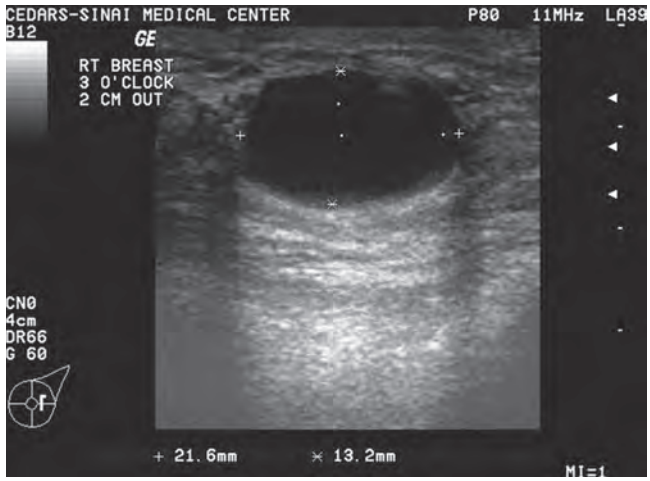
Clinically, women present with a mass that produces significant anxiety and can be hard to distinguish from cancer. Mammography may be normal in these patients, and there are no specific radiographic criteria that help to distinguish this entity. Ultrasound is the most useful test in differentiating a cyst from a solid mass (Fig. 16.3A & B). Findings on ultrasound characteristic of a simple cyst include a round lesion with smooth borders, posterior acoustic enhancement, and absence of internal echoes. If ultrasound findings are not classic for a simple cyst and demonstrate internal septations within the cyst, the cyst is classified as a complex cyst, and FNA or CNB should be performed for diagnosis.

Most patients need reassurance and do not require further treatment after ultrasound confirmation of a simple cyst or for cyclical pain with no findings. Aspiration of a simple cyst is only performed if a patient is symptomatic. Aspiration is usually performed with an 18- or 20-gauge needle, and if nonbloody fluid is aspirated, the fluid is not sent for cytology. If aspiration results in complete resolution of the cyst, patients can be clinically followed. If under ultrasound guidance the cyst continues to recur despite repeated aspirations, a mass is noted after aspiration of the cyst, or if bloody fluid is aspirated, needle biopsy or excision is recommended due to the risk of atypia or malignancy.

Dietary modulation and nutritional supplements have been investigated in providing symptomatic relief. The role of caffeine and other caffeine-containing products including tea and chocolate in accentuating pain remains controversial.[90,91] Some patients do report pain relief after discontinuing caffeine-containing products. Similarly, observational studies have shown vitamin E (600 IU daily) or B6 (200 to 800 mg/day) may be helpful in reducing symptoms.[92,93]

Fibrocystic Changes and Cancer Risk

Fibrocystic change that demonstrates apocrine changes with mild epithelial hyperplasia of usual type does not increase future risk of breast cancer; however, moderate or florid hyperplasia with or without atypia on biopsy is associated with an increased risk of breast cancer.[94,95] Women with proliferative changes and no atypical hyperplasia have a two-fold risk of developing breast cancer. Patients with biopsies that demonstrate proliferative changes with atypical hyperplasia have a four- to five-fold risk of developing breast cancer in either breast. A family history of breast cancer in a patient with cysts and proliferative changes increases the risk three-fold. Women with proliferative changes and family history should be followed with clinical breast exams and mammography annually.



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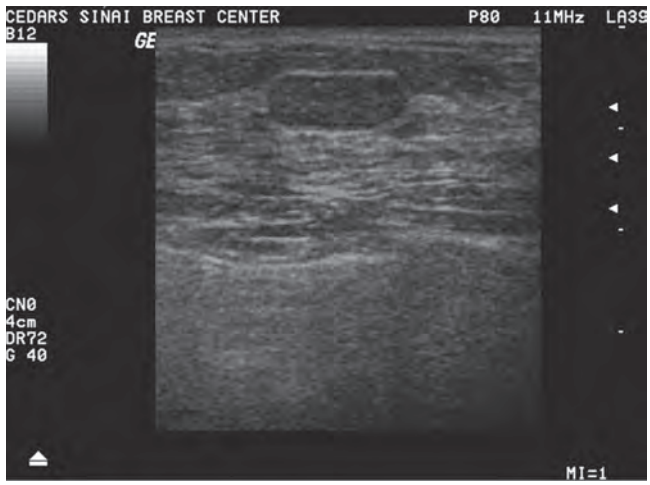

B

FIGURE 16.3 **A:** Ultrasound demonstrating a simple cyst. **B:** Ultrasound demonstrating a solid mass.

Mastalgia

Breast pain remains one of the most common reason patients seek medical care due to concerns about risk of breast cancer. It is a physiologic symptom that frequently occurs in the luteal phase of the menstrual cycle. Localized breast pain may be the only presenting symptom in up to 15% of women with newly diagnosed

breast cancer.[96] Research has focused on abnormal levels of estradiol, progesterone, and prolactin as possible causes of mastalgia; however, no consistent findings have been observed.[97–99] Inflammatory cytokines, interleukin-6, and tumor necrosis-α have also been implicated; however, no differences in expression have been seen in breast tissue from women who have no pain when compared to breast tissue from women who have mastalgia.[100]

Classification of Mastalgia

Mastalgia is classified as either cyclical or noncyclical. Cyclical mastalgia occurs in the luteal phase of the menstrual cycle, and patients present with bilateral breast engorgement, pain, and tenderness. These findings are more prevalent in women in the third and fourth decade of life. Noncyclical mastalgia is unilateral and independent of the menstrual cycle and usually occurs in the fourth to fifth decade of life. It is described as a burning, stabbing-like pain that can last for a few minutes or last for several days. Symptoms tend to be independent of the menstrual cycle.

Management of Mastalgia

Once patients have had a clinical breast exam and appropriate breast imaging, and malignancy is excluded, patients usually respond to reassurance and require no further treatment. For some patients who experience severe mastalgia, anxiety and depression are common.[101,102]

Dietary modifications including reducing caffeine and saturated fat intake have not been shown to improve symptoms. The data on evening primrose oil remains controversial, with most studies demonstrating no benefit in reducing pain or premenstrual symptoms when compared to placebo.[103–105]

Danazol, a synthetic androgen, is the only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of mastalgia. Side effects include hirsutism, acne, weight gain, depression, headaches, and menstrual irregularities. A double-blinded placebo-controlled trial of 100 women with severe mastalgia and premenstrual symptoms reported a 79% reduction in mastalgia in patients treated with danazol compared to 23% in the placebo group; however, the authors report no improvement in premenstrual symptoms.[106] This drug is rarely used because of its side effects.

Prolactin levels have been reported to be elevated in patients with mastalgia. Bromocriptine, a dopamine antagonist has been shown to reduce prolactin levels. Rea et al.[107] treated 36 women with moderate to severe cyclical mastalgia who had normal levels of prolactin. Patients were given intravenous thyrotropin-releasing hormone, and were classified into two groups. The first group had elevated levels of prolactin and consisted of 19 patients. The second group had normal levels of prolactin. All patients were given bromocriptine for 3 to 6 months. Overall, 73.6% of patients with elevated prolactin levels and 23.5 % of patients with normal prolactin levels ($p < 0.05$) reported symptomatic relief; however, most patients were unable to continue the study due to the side effects of nausea, vomiting, and headache associated with taking the drug.

Several investigators have also proposed the use of tamoxifen, a selective estrogen receptor modulator, which is used in the treatment of hormone receptor–positive breast cancer, for the treatment of cyclical mastalgia rather than noncyclical mastalgia. Women given doses of 10 or 20 mg have been shown to have significant symptomatic pain relief when given for 3 to 6 months.[108,109] The protracted use of tamoxifen for cyclical mastalgia has not been studied because of the long-term side effects with use of this drug. Toremifene citrate, a member of the selective estrogen receptor modulators with fewer side effects than tamoxifen, has also been studied in patients with cyclical and noncyclical mastalgia. Gong et al.[110] performed a double-blind randomized controlled clinical trial in patients with moderate to severe mastalgia. Patients with cyclical mastalgia who received 60 mg of toremifene demonstrated a rapid reduction in pain scores (52%) within 30 days compared to the placebo arm (20.2%, $p < 0.001$). This effect was also observed through days 60 and 90 of the study period. The incidence of adverse events, which included menstrual disturbances, dizziness, and nausea were similar between both groups; however, patients in the treatment arm had a slightly higher incidence of vaginal discharge. The use of toremifene for longer duration has not been reported. Drugs are rarely used to treat mastalgia except occasional mild analgesics.

Fibroepithelial Lesions

Fibroadenoma

Fibroadenomas are the most common benign solid tumor of the breast. These lesions usually occur in women in their second and third decade of life but have also been found in women in their 40s and 50s.[111] Clinically, these patients present with a nontender, round, mobile solid mass. Imaging findings demonstrate typical features of a well-defined, smooth, solid mass with defined margins. Most lesions are between 1 and 3 cm in size and do not change in size; however, 15% of lesions regress spontaneously, with studies demonstrating up to 10% of lesions to increase in size.[112–114] Fibroadenomas with characteristic findings on imaging can be followed clinically with observation, CNB can be performed to confirm diagnosis, or the lesion can be excised based on patient preference. Fibroadenomas are not associated with an increased risk of breast cancer, and carcinoma arising within a fibroadenoma is rare.[115] Excision is recommended if the lesion grows or is larger than 3 cm in size, which may be hard to distinguish from a benign

phyllodes tumor based on imaging. Histologically, fibroadenomas are pseudoencapsulated and can be sharply delineated from the surrounding breast parenchyma and they have both an epithelial and a stromal component.

Multiple fibroadenomas have been known to occur in about 15% of women and should be managed similarly to patients with a single lesion. Excision of multiple lesions can leave significant breast deformities and does not prevent the formation of new lesions.

Phyllodes Tumor

Phyllodes tumors are fibroepithelial lesions that range clinically and histologically from benign to malignant. Benign lesions are more commonly seen in women between the third and fifth decade of life. Clinically, these lesions are difficult to distinguish from a fibroadenoma; however, patients do describe initial stability with the lesion followed by a period of rapid growth. Although these lesions can be as small as fibroadenomas, they can rapidly grow and occupy the entire breast.[116,117]

Mammography and ultrasonography do not have characteristic features that can reliably distinguish a phyllodes tumor from a fibroadenoma.[118] Histologic distinction can also be difficult to ascertain from a CNB. Phyllodes lesions are stratified based on stromal cellularity and overgrowth, number of mitoses per high-power field, infiltration of the surrounding parenchyma, and cellular atypia.[119,120]

If a lesion does not clearly fit criteria for a fibroadenoma, then surgical excision is recommended. These criteria include any of the following: a lesion that cannot be classified as a fibroadenoma on CNB, lesions with rapid growth, those larger than about 3 cm, those with mammographic or ultrasound features that are not classic for a fibroadenoma, and those that demonstrate a lobulated lesion or intramural cysts on ultrasonography. If a patient desires observation, short interval follow-up of 3 to 6 months is recommended. Surgical excision alone is recommended for a biopsy-proven benign phyllodes tumor. Mastectomy may have to be performed for large lesions in relatively small breasts. Axillary staging is not indicated. Prognosis in patients with phyllodes tumors is variable. Benign phyllodes tumors locally recur in up to 10% of patients who undergo surgical excision.[121]

Malignant phyllodes tumors behave similar to sarcomas, tend to recur locally, and have also been known to metastasize to the lung, bone, and brain.[122,123] Unlike benign phyllodes tumors, malignant lesions need to be excised with at least tumor-free margins. Positive histologic margins have been associated with a risk of local recurrence and are an independent predictor of lower disease-free survival.[124,125] Radiation may be used for patients with large tumors, tumors that recur, and patients with positive margins. Chemotherapy is used for metastatic disease, and regimens are based on management of sarcoma patients. Metastases from malignant phyllodes tumors are unusual.

Fat Necrosis

Fat necrosis resulting from adipose tissue saponification in the breast occurs after trauma or commonly after surgery. It may present as a mass mimicking the appearance of a malignancy on physical exam and imaging. Patients who have a history of trauma may have ecchymosis on physical examination. Imaging findings are nonspecific and may present either as an oil cyst, calcifications, or fibrosis that can appear as a speculated mass on mammography. CNB or excision may be required for definitive diagnosis.

Nipple Discharge

Nipple discharge occurs in about 5% of patients who present for an evaluation of breast symptoms. Almost an equal number of patients present with spontaneous and provoked nipple discharge. Provoked or self-induced nipple discharge usually has no underlying pathologic significance, and patients are managed with reassurance and encouraged to stop manipulating the nipple. Spontaneous nipple discharge is more likely to be associated with underlying disease. Most studies report spontaneous nipple discharge to be associated with an underlying malignancy in 5 to 10% of patients.[126,127]

Clinical evaluation should include the nature of the discharge (serous, bloody, or milky), involvement of single or multiple ducts, unilateral or bilateral breast involvement, palpation of an underlying mass, menopausal status of the patient, relationship of discharge to menses if patient is premenopausal, or if the patient is on hormonal therapy.

Unilateral bloody nipple discharge is usually caused by an intraductal papillary lesion. Fibrocystic changes usually result in unilateral or bilateral green or brown discharge in premenopausal women. Galactorrhea usually stops within a year after nursing has been discontinued, but it may last longer. Milky discharge in nonlactating women should prompt evaluation of serum prolactin to detect a pituitary prolactinoma and thyroid-stimulating hormone levels to rule out hypothyroidism, which can cause galactorrhea. Oral contraceptives can cause serous discharge from multiple ducts usually before the start of menstruation. Phenothiazines have also been shown to cause nipple discharge, which usually stops once the drug is discontinued.

Cytology of nipple discharge may show abnormal cells but is not useful in the management of these patients. Ductography can be performed to identify a central filling defect or abrupt termination of dye in a ductal system suggesting an intraductal lesion; however, it is painful and usually not helpful for management. Fiberoptic ductoscopy may result in successful identification of a papillary lesion in 35 to 40% of patients but is generally not performed.[128,129] Mammography and ultrasound are also performed to identify central or peripheral lesions.

Surgical excision is recommended for spontaneous unilateral, single duct nipple discharge that is copious or bloody. Patients should be counseled prior to the operation regarding changes in nipple sensation, deformity, and potential inability to breast-feed after surgical excision. Excision is performed through a circumareolar incision. The duct may be cannulated and methylene blue injected allowing identification of the affected ductal system. Excision of the draining ductal system is performed over a distance of 3 to 5 cm distally into the breast parenchyma. Once excision is performed, the nipple should be manipulated to ensure no bloody fluid can be elicited, providing confirmation that the diseased duct has been excised.

Mastitis/Breast Abscess

Breast infections are rare and tend to occur in women who are lactating. Lactational mastitis usually occurs from breakdown of skin or cracking of the nipple resulting in bacterial translocation into the breast. Patients with mastitis are initially noted to have fever, erythema, tenderness, and swelling. Patients with an abscess present with a tender underlying palpable mass with fluctuance and systemic signs of infection with leukocytosis, fever, and tachycardia. The organism most commonly found in these infections is *Staphylococcus aureus*.[130] Mastitis can be treated with dicloxacillin, and women can continue to breast-feed while on dicloxacillin. They are also encouraged to apply warm compresses and manual pressure to the area. If patients do not respond, an ultrasound should be performed to exclude an abscess. Aspiration of a breast abscess can be performed if the overlying skin does not appear thin and shiny. Aspiration and antibiotics are usually successful in resolving small abscesses. For large abscesses or if the skin is affected, incision and drainage should be performed under local anesthesia.

Nonlactational Abscess

Nonlactational breast abscesses are rare and are usually seen in patients who have diabetes, prolonged steroid treatment, or trauma. *S. aureus* is the most common organism; however, mixed anaerobic organisms have also been identified.[131] Patients should be treated conservatively with antibiotics; however, if an ultrasound demonstrates an abscess, aspiration or incision and drainage should be performed. If erythema of the breast persists without the presence of abscess cavity on ultrasound, punch biopsy of the skin should be performed to rule out inflammatory carcinoma.

Nipple Inversion

Nipple inversion may affect one or both breasts, and it may be congenital or acquired. Benign inversion of the nipple usually occurs gradually over the course of a few years. If inversion occurs rapidly, the underlying cause may include mammary duct ectasia, postsurgical changes, periductal mastitis, fat necrosis, or it may represent an underlying malignancy.[132] A complete breast examination, accompanied with imaging, should be done to look for the underlying cause.

MALIGNANT BREAST DISEASE

Breast cancer is the most common malignancy in women and the second leading cause of death from malignancy after lung cancer. Each year, over 230,000 women are diagnosed with invasive breast cancer, and an additional 55,000 women are diagnosed with in situ breast cancer.[133] Over the last three decades, evidence from large randomized clinical trials have brought about major changes in the management of patients with breast cancer. Screening mammography, advances in both adjuvant systemic chemotherapy and radiation treatment, the implementation of breast conservation surgery, and sentinel node biopsy (SNB) have substantially impacted the management of these patients.

Pathology

Invasive breast cancers can be divided into two histopathologic subtypes: invasive ductal carcinomas and invasive lobular carcinomas. Invasive ductal carcinomas (IDCs) comprise the vast majority, about 80 to 85%, of all breast cancers.[134] The remaining 15 to 20% of breast cancers is composed of lobular cancers or other more rare variants.

Ductal carcinomas, in their earliest forms, exist as in situ disease, where epithelial proliferation has not invaded into the stroma and the basement membrane remains intact.[135] The natural history of DCIS is poorly understood because treatment strategies have usually involved early wide local excision or mastectomy, but DCIS is generally thought of as a precursor lesion for IDCs.

Various morphologic subtypes of IDC include medullary, mucinous, tubular, and scirrhous carcinoma. Medullary breast cancers, comprising 3 to 6% of all invasive breast cancers, classically exhibit a lymphocytic infiltrate of the tumor stroma with solid sheets of large, pleomorphic cells causing a syncytial appearance.[136] Despite this rather aggressive histologic appearance, medullary breast cancers have a better prognosis than other breast cancers with an 85% 5-year overall survival rate compared to a 63% overall survival of nonmedullary breast cancers due to slow-growing and less aggressive biology.[137]

Mucinous carcinomas are another subtype of IDC which has a characteristic grossly mucinous but histologically acellular appearance of at least 50% of the cancer. These cancers account for about 1 to 4% of all breast cancers and have a favorable outcome compared to IDC.[138]

Tubular carcinomas of the breast account for about 1% of all IDCs and are an indolent subtype of breast

cancer. About 5% of patients with tubular carcinoma will have a metastasis to the axillary lymph nodes.[139]

Breast cancer is a molecularly heterogeneous disease, and through the use of gene expression profiling, breast cancers are now classified into at least four biologically distinct subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2/neu) overexpressing, and basal-like.[140] These subtypes differ with regard to their patterns of gene expression, clinical features, response to chemotherapy, and outcome. Luminal A and B cancers, which account for about 70% of all breast cancers show high expression of the hormone receptors, estrogen receptor (ER) and progesterone receptor (PR), and associated genes, and generally have a good prognosis. The luminal B cancers tend to be higher grade than the luminal A cancers and some overexpress HER2/neu. In addition, luminal A cancers respond better to endocrine therapy than luminal B cancers. The HER2/neu cancers, which account for about 15% of all cancers, show high expression of HER2/neu and low expression of ER and PR. These cancers are more likely to be high grade. These cancers respond to trastuzumab and to anthracycline-based chemotherapy regimens. The basal-like breast cancers (BLBCs) show high expression of basal epithelial genes and basal cytokeratins, low expression of ER/PR as well as low expression of HER2/neu. They constitute approximately 15% of all breast cancers and are often referred to as the triple-negative phenotype because they are invariably ER, PR, and HER2/neu negative.

Staging

Breast cancer may be conceptually approached by considering the local process of the cancer arising in the breast and the systemic process of metastasis. Local breast cancer growth is largely dependent on the biology of the tumor which is influenced by several factors, including histology, genetic background of the individual patient, and genomic receptor status. Much of the surgical treatment of breast cancer focuses on controlling local disease. Nonetheless, breast cancer has the ability to metastasize to other organs, most commonly to liver, lungs, or bone. The growth rate of breast cancer varies from tumor to tumor and patient to patient. If a breast cancer cell had a consistent doubling time of 100 days, the tumor would reach a 1 cm diameter in 8 years.[141] Indeed, it is known that in the relatively long preclinical phase of breast cancer, before the breast cancer is clinically evident, tumor cells are likely circulating in the body. Thus, there is ample opportunity for possible metastatic spread of breast cancer even in patients with early disease. Nonetheless, many factors also contribute to the ability of breast cancer to metastasize to other organs. In the treatment of breast cancer, optimizing treatment for both local and possible future systemic disease must be considered.

In order to determine the optimal treatment course to maximize overall survival, clinical staging and pathologic staging are of utmost importance. The American Joint Committee of Cancer tumor-node-metastasis system is the current standard for preoperative clinical and postoperative pathologic staging (Tables 16.4 and 16.5) which incorporate size of the tumor, nodal disease, and metastatic disease into the staging system.[142]

Preoperative Evaluation

For patients with malignancy on core biopsy and initial clinical staging reveals an early stage I cancer with no other evidence of disease in the lymph nodes or abdomen by clinical examination, the patient should undergo bilateral diagnostic mammography, a chest x-ray, and blood tests including a complete blood count and complete metabolic panel. If there is evidence of an abnormality on chest x-ray or blood tests, further imaging modalities should be ordered such as bone scan, chest and abdominal computed tomography (CT) scans, or MRI. Otherwise, further imaging studies are usually not necessary unless there are specific patient symptoms.

Patients with clinical stage II/III disease with clinically node-positive disease are recommended to undergo bone scan; CT scan imaging is ordered if other preoperative testing is found to be abnormal. Patients with more advanced clinically stage III or IV disease should undergo further staging imaging studies including bone scan to evaluate for bone metastasis and CT scan of the abdomen to evaluate for liver metastasis. Combined positron emission tomography (PET)/CT scan is an additional modality that is used to stage advanced breast cancer and to evaluate patients at high risk for recurrence; however, it is unclear whether this test should be used to stage early breast cancers. Nonetheless, PET scan alone has a high sensitivity and specificity in detecting breast cancer metastasis. In one study of 118 patients, PET scan was found to have a sensitivity of 87% and specificity of 83% which compared favorably to CT scan with a sensitivity of 83% and specificity of 85%.[143] Another study investigating combined PET/CT scan found that for 154 initial stage II or III breast cancer patients, a combination of PET/CT had a sensitivity of 100% and specificity of 95% suggesting that combined PET/CT may be superior to conventional imaging.[144] A more recent prospective study showed a possible role for combined PET/CT in staging even early breast cancers.[145] However, further studies will need to be performed to ascertain the true value of these newer imaging modalities.

Breast Cancer Treatment

Breast cancer is treated with surgery, radiation, and systemic (chemotherapy, hormonal, targeted) chemotherapy in varying combinations and sequences. Thus, like many modern treatments of cancers, it is treated in a true

TABLE 16.4 Tumor–Nodes–Metastasis System for Staging of Breast Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to chest wall and/or skin (ulceration or skin nodules)
T4a	Extension to chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional Lymph Nodes (N)	
Clinical	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases to ipsilateral level I, II axillary lymph node(s) that are clinically fixed or matted, or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph nodes and with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
Pathologic Classification (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
$pN0_{(i-)}$	No regional lymph node metastases histologically, negative IHC
$pN0_{(i+)}$	Malignant cells in regional lymph node(s) not greater than 0.2 mm (detected by H&E or IHC including ITC)
$pN0_{(mol-)}$	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
$pN0_{(mol+)}$	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in one to three axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastasis (>0.2 mm and/or more than 200 cells but none >2.0 mm)
pN1a	Metastases in one to three axillary lymph nodes, at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically apparent
pN1c	Metastases in one to three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in four to nine axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in four to nine axillary lymph nodes (at least one tumor deposit >2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases

TABLE 16.4 Tumor–Nodes–Metastasis System for Staging of Breast Cancer *(Continued)*

pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastasis to the infraclavicular (level III axillary) lymph nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular node(s)
Distant Metastasis (M)	
M0	No clinical or radiologic evidence of distant metastasis
cM0$_{(i+)}$	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are not larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

IHC, immunohistochemical; H&E, hematoxylin and eosin stain; ITC, isolated tumor cell; RT-PCR, reverse transcriptase/polymerase chain reaction.
From Edge SB, Byrd DB, Compton CC, et al, eds. *Breast*. In: *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010:419–460, with permission.

collaborative multimodality fashion. Surgical treatment of breast cancer has continually evolved from invasive and disfiguring operations to more conservative ones because of the benefit of data from several early clinical trials. Historically, radical mastectomy was performed for operative candidates with breast cancer during which the entire breast was removed along with the underlying pectoral muscles and the axillary and sometimes internal mammary lymph nodes.[146] This radical surgery was performed with disfiguring and debilitating results. Thus, the modified radical mastectomy was introduced, which consists of removing the breast and axillary lymph nodes but sparing the pectoralis muscles with more limited removal of skin and lymph nodes. The landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial compared patients receiving radical mastectomy, total mastectomy with radiation, and mastectomy alone. The trial showed no difference in survival among the arms but did show an increase in local and regional control in the radiation arms.[147] This trial established that survival is equivalent comparing radical mastectomy to modified radical mastectomy, with modified radical mastectomy patient having better cosmesis and function.

TABLE 16.5 Staging of Breast Carcinoma Anatomic Stage/Prognostic Groups

	TNM Classification		
	Tumor	**Node**	**Metastasis**
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1$_{mi}$	M0
	T1*	N1$_{mi}$	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

*T$_1$ includes T$_{1mi}$.
**T0 and T1 tumors with nodal micrometastases only are excluded from stage IIA and are classified stage IB.
From Edge SB, Byrd DB, Compton CC, et al., eds. *Breast*. In: *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010:419–460, with permission.

In addition, subsequent randomized control studies showed postmastectomy radiation did reduce the risk of local-regional failure by 20% and produced an absolute survival benefit of 10% at 10 years in stages II and III breast cancer patients.[148–150] Thus, guidelines were established from the American Society of Clinical Oncology (ASCO) to recommend radiation as an adjuvant for patients with large breast cancers greater than 5 cm in diameter and for patients with four or more positive axillary lymph nodes.[151]

Breast conservation therapy with lumpectomy and radiation continued to evolve with the results of the NSABP B-06 and the Milan quadrantectomy trial. In NSABP B-06, patients with stage I or II breast cancers were randomized to modified radical mastectomy, segmental mastectomy with axillary lymph node dissection or segmental mastectomy with axillary lymph node dissection and postoperative radiation therapy.[152] There were no significant differences in overall survival among the three groups. There was a slight trend toward

improved survival in the patients who had received radiation after lumpectomy compared to lumpectomy alone. The local recurrence rates were lower for the lumpectomy patients who had received radiation. This study and others showed that lumpectomy or partial mastectomy with axillary lymph node dissection was as effective as modified radical mastectomy and paved the way toward current breast conservation treatments.

Operative treatments further evolved into more minimally invasive techniques with the development of the sentinel lymph node biopsy procedure. Traditionally, axillary lymphadenectomy, where all of the levels I and II axillary lymph nodes are surgically removed, was used to stage and treat operable breast cancers.[153] The procedure is important for locoregional control because regional recurrence rates are low, ranging from 1 to 3%. Nonetheless, the procedure can cause significant morbidities because anywhere from 6 to 30% of patients can have chronic lymphedema and 30% of patients can have acute complications.[154,155]

In order to address these problems, a method of lymphatic mapping and sentinel lymph node biopsy was developed in 1991.[156] Dye and isotope studies showed that breast cancer spreads to the lymph nodes by starting in only one or two of the initial nodes. The first lymph node encountered, draining the lymphatic channels from the tumor to the axillary basin, is the sentinel lymph node. Thus, the breast cancer is most likely to metastasize to that lymph node. By performing lymphoscintigraphy and/or injecting a dye intraoperatively to map the draining lymph nodes, the sentinel lymph node can be identified and excised.

Several studies have shown that the sentinel lymph node technique accurately stages the axilla with successful identification of the sentinel lymph node in 90 to 99% of the studies and a false-negative rate of less than 5%.[157–160] Accordingly, sentinel lymph node biopsy has replaced axillary lymph node dissection as a first procedure in patients with nonpalpable axillary disease. If the sentinel lymph node is found to be positive, patients usually have a completion axillary lymph node dissection. In patients with palpable axillary disease, an ultrasound and FNA are usually performed to confirm the diagnosis of advanced cancer, and the patient will usually have a complete axillary lymph node dissection as the first surgery of choice to treat the axilla.

Recently, the Z0011 randomized controlled trial of the American College of Surgeons Oncology Group (ACOSOG) provided evidence that completion axillary lymph node dissection is not necessary in sentinel lymph node–positive patients with small T1 or T2 tumors with clinically nonpalpable axillary lymph nodes. This trial randomized 891 women into receiving completion axillary lymph node dissection or observation after a sentinel lymph node biopsy showing lymph node metastasis shown by hematoxylin and eosin staining and found that foregoing completion axillary lymph node dissection did not result in inferior survival.[161] Nearly all patients received whole breast radiation and systemic therapy. Many cancer centers are now limiting the use of completion lymph node dissection in patients with small tumors with positive sentinel lymph nodes based on the results of the Z0011.

Adjuvant System Treatment

Although it is important to rigorously treat the local disease of breast cancer in the breast and axilla, breast cancer is often a systemic disease at the time of diagnosis despite no clinical evidence of metastasis. Adjuvant systemic therapy for many patients is a crucial step in their treatment plan. Adjuvant therapy serves to treat any occult metastatic disease that may be harbored in the patient and improves survival.

Adjuvant systemic therapy provides decreases in risk of death by about 25% per year in breast cancer patients.[162] If the patient has a small, low-grade tumor with low chance of recurrence, the risks of undergoing systemic chemotherapy may outweigh the potential benefit of chemotherapy for that patient. Thus, the absolute risk reduction for patients who have a low risk of recurrence to begin with may be negligible, whereas patients with a high risk of recurrence may have up to a 30% risk reduction of recurrence and metastatic disease. Thus, choosing breast cancer patients who will benefit from adjuvant therapy is critical. Patient whose risk of relapse is greater than 10% at 10 years are recommended to undergo adjuvant systemic therapy.

Different patient characteristics and tumor factors must be considered when evaluating patients for possible adjuvant therapy. Factors that may increase the risk of recurrence include size of T2 or greater, negative hormone receptors, positive biological receptors such as HER2/neu, nuclear and histologic grade, and proliferation rate.[163] In addition, lymph nodes status is critical when discussing recurrence risk. Patients with positive lymph node disease have a higher risk of recurrence. In addition, patients with larger primary tumors have an increased risk of recurrence and decreased overall survival (Table 16.6). One study showed the risk of recurrence of a greater than 3 cm breast tumor is 27% at 10 years, but patients with a less than 1 cm tumor had a 9% risk of recurrence.[164]

The tumor receptor status is also critical in predicting the recurrence risk of a tumor. Estrogen and progesterone hormone receptor status are routinely tested on the specimens. Many studies have shown an improved overall survival in patients with positive hormone receptors.[165,166] HER2/neu-positive cancers in the past carried a worse overall prognosis based on their biology before the monoclonal antibody treatment trastuzumab (Herceptin) was available.

TABLE 16.6 Year Survival According to Stage of Breast Cancer

AJCC Stage	5-Year Survival (%)	10-Year Survival (%)
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, Hurvitz SA. *Breast Disorders*. In: McPhee SJ, Papadakis MA, eds. *2011 Current Medical Diagnosis and Treatment*. New York: McGraw-Hill; 2011, with permission.

Recently, multigene assays estimating a patient's breast cancer risk have been used to identify patients at risk for recurrence. The Oncotype Dx and Mammaprint assays can identify negative lymph node and positive estrogen receptor patients who still may benefit from adjuvant therapy. The Oncotype Dx uses a 21-gene assay to calculate a recurrence score from 0 to 100 for each individual patient and has been validated in multiple studies.[167-169] The test assumes that the patient will be on 5 years of adjuvant hormonal therapy and calculates the 10-year risk of metastatic disease. In addition, the Mammaprint assay similarly predicts distant metastasis using a 70-gene assay.[170] These tests add to the clinical and pathologic prognostic factors that determine the likelihood of recurrence increasing the tools in our armamentarium to predict who may best benefit from adjuvant therapy. It is recommended that node-negative patients or patients with positive lymph nodes with metastatic deposit of 2 mm or less or with invasive breast cancer greater than 0.5 cm in diameter undergo testing with the 21-gene assay to ascertain a need for adjuvant chemotherapy. Hormone therapy is recommended for a low-risk score of less than 18. Hormone therapy with or without chemotherapy may be considered for an intermediate score between 18 and 30. Adjuvant chemotherapy with hormone therapy is recommended for patients with a high-risk score greater than 30 and for patients with lymph node tumor deposits greater than 2 mm.

The best chemotherapeutic regimens have evolved and continue to evolve with the data from several randomized clinical trials over time. Initially, the most common combination therapy was cyclophosphamide, methotrexate, and 5-flourouracil (CMF). This regimen, given in 12 monthly cycles, was found to have a statistically significant survival benefit in premenopausal patients and especially in patients with node-positive disease.[171] This survival advantage was shown to continue to be borne out after 20 years of follow-up in premenopausal patients and, in another study, was shown to extend to both premenopausal and postmenopausal estrogen-receptor and node-negative patients who after being treated with CMF showed a 71% versus 48% disease-free survival advantage after 12 years of follow-up.[172,173]

CMF then was largely replaced by doxorubicin (Adriamycin)-based regimens based on large randomized trials such as the NSABP B-15 study comparing CMF and Adriamycin and cyclophosphamide (AC) showing equivalency and the shorter duration of treatment of about 4 months with the AC regimen.[174] Subsequently, the taxane class of chemotherapeutics including paclitaxel and docetaxel were shown to have better efficacy with a 17% improvement in recurrence and 18% reduction of death when paclitaxel was added to cyclophosphamide.[175] In addition, the U.S. Oncology Research Group Trial 9735 showed an improved disease-free and overall survival when comparing docetaxel and cyclophosphamide (TC) to traditional AC.[176] The advantages of a nonanthracycline-based chemotherapy regimen are that it eliminates the side effects of cardiotoxicity and leukemia. Currently, the preferred chemotherapy regimens for HER2/neu-negative breast cancers according to the 2012 National Comprehensive Cancer Network (NCCN) guidelines for breast cancer consist of the docetaxel, doxorubicin, cyclophosphamide (TAC) regimen, the dose-dense AC regimen followed by paclitaxel chemotherapy, AC followed by paclitaxel, or TC chemotherapy.[177-179] A recent meta-analysis of six randomized clinical trials using trastuzumab as part of adjuvant treatment found that there was a statistically significant benefit in disease-free survival, overall survival, locoregional recurrence, and distant recurrence.[180] With the use of trastuzumab for HER2/neu-positive breast cancers, an additional 1-year course of trastuzumab is recommended in addition to combination chemotherapy.

Hormonal therapies are an important adjuvant treatment in estrogen receptor–positive women. Tamoxifen or an aromatase inhibitor decreases the risk of breast cancer recurrence. A 5-year course of tamoxifen can reduce the local recurrence by 50%, the overall survival by 25%, and improved disease-free survival in node-negative patients after 5-year follow-up.[181] NSABP B-14 showed that 10-year survival in both premenopausal and postmenopausal women was improved 82 and 79%, respectively.[182] Aromatase inhibitors (AIs) such as anastrozole (Arimidex) or letrozole (Femara) blocks aromatase which converts androgens into estrogens. AIs tend to cause significant side effects such as osteoporosis, hot flashes, endometrial cancer, and muscle aches and pains. Nonetheless, AIs have been found to result in lower overall recurrence and contralateral breast tumors in the Arimidex, tamoxifen, alone or in combination (ATAC) trial.[183] Another study showed that switching patients to an AI after tamoxifen therapy may further

improve survival.[184] A subsequent update to the Breast International Group (BIG) 1-98 randomized controlled trial comparing postmenopausal women with endocrine-responsive breast cancer treated with sequential tamoxifen and letrozole therapy compared to 5 years of letrozole or tamoxifen monotherapy found that sequential therapy did not add any benefit to disease-free survival compared to letrozole monotherapy.[185] Thus, AI therapy should be considered first-line therapy for postmenopausal women. Nonetheless, in patients with significant osteoporosis, either concomitant therapy with a bisphosphonate such as zoledronic acid or a switch to tamoxifen should be considered, because AI therapy is associated with a higher incidence of osteoporosis and bone fractures compared to tamoxifen. Tamoxifen carries a higher risk of the development of endometrial cancer and is contraindicated in patients who have a risk of that disease.

Neoadjuvant chemotherapy may be considered in women who desire breast conservation therapy. Updates to the ongoing NSABP B-18 trial, which evaluated preoperative or postoperative AC, and NSABP B-27 trial, which examined the role of adding docetaxel to AC, both demonstrated that preoperative therapy was equivalent to postoperative therapy but not better. Taxanes enhanced response and decreased cumulative incidence of local recurrence when added to AC. In a 9-year follow-up to the B-18 trial, overall survival and disease-free survival continued to be equivalent, whereas the preoperative chemotherapy group had a higher chance of breast conservation. An evaluation and biopsy of the tumor should be performed prior to the initiation of neoadjuvant therapy to determine whether the patient is a suitable candidate for breast conservation and to assess the need for sentinel lymph node biopsy or FNA of the axilla prior to beginning treatment. Neoadjuvant hormonal and endocrine therapy is also an option for selected patients. The Immediate Preoperative Arimidex Alone or in Combination with Tamoxifen study (IMPACT) compared patients receiving anastrozole or tamoxifen or a combination of both drugs in 3-month neoadjuvant regimens where the patients continued on these regimens postoperatively for 5 years.[186] The patients were found to have similar clinical response rate, although the anastrozole-treated patient had a statistically significant more conservative surgery compared to the tamoxifen arm. The Preoperative Arimidex Compared to Tamoxifen (PROACT) trial compared 12 weeks of neoadjuvant anastrozole versus tamoxifen therapy.[187] Response rates by ultrasound were found to be similar for both drugs. Thus, compared to adjuvant treatment trials in the neoadjuvant setting, AIs are not found to be superior in terms of response rates compared to tamoxifen. Neoadjuvant hormonal treatments are generally reserved for patients with hormone-sensitive tumors who are postmenopausal.

Finally, given the plethora of adjuvant and neoadjuvant therapies available, currently, oncologists must evaluate the patient and the breast cancer characteristics and decide which chemotherapeutic and/or hormonal regimen is optimal for each individual patient.

BREAST CANCER IN PREGNANCY

Breast cancer is the second most common cancer encountered during pregnancy. Fortunately, stage for stage, breast cancer during pregnancy has the same prognosis when matched to breast cancer patients who are not pregnant. Nonetheless, the timing of the pregnancy plays a critical role in deciding the sequence of treatment. Patients should all undergo bilateral ultrasound and mammography; FNA and/or core biopsy should be performed to obtain a diagnosis and hormone receptor information.

Pregnant women are often concerned about the risk of miscarriage associated with surgery. In a review of the literature, Cohen-Kerem et al.[187] found that overall, 5.8% of pregnancies ended in miscarriage in women who had any surgical intervention (not just those related to breast cancer) at any point in pregnancy. Where the trimester of pregnancy was indicated in the papers they reviewed, the rate of miscarriage in the first trimester was 10.5% for women undergoing any surgical intervention.[188]

Chemotherapy for breast cancer cannot be administered in the first trimester given the significant risk of birth defects. Thus, the patient may consider aborting the fetus or undergoing surgical treatment such as a modified radical mastectomy understanding the likelihood of miscarriage. In the second trimester, both surgical and chemotherapeutic strategies should pose a smaller risk to the fetus, and both a modified radical mastectomy and neoadjuvant chemotherapy are reasonable alternatives.[189] Sentinel lymph node biopsy can be performed; however, blue dye is not recommended in the pregnant patient. However, radiocolloid appears to be safe in pregnant patients.[190] Breast conservation therapy is difficult to perform in the second trimester due to the risk of a significant delay that would need to occur to undergo radiation therapy. Nonetheless, patients will often undergo a course of adjuvant chemotherapy in the second trimester before radiation therapy commences. Currently, chemotherapy is considered safe for the fetus after 14 weeks' gestation with no association with congenital anomalies.[191] However, an increased incidence of intrauterine growth restriction, hematopoietic abnormalities, and neonatal prematurity and death have been reported.[192] Thus, neoadjuvant chemotherapy is also recommended in selected patient cases after 14 weeks of pregnancy. Breast conservation is an option in the latter half of the third trimester because radiation can be delayed until after delivery.

CLINICAL NOTES

- Evaluate all breast complaints thoroughly in order to diagnose and promptly treat benign breast lesions, as well as malignancies.
- A complete history should be taken of each woman with a breast complaint, including maternal and paternal family histories and past or present lifestyle behaviors as well as medical and surgical events.
- Examination of the breast should be done in both the seated and supine positions.
- Lesions noted on examination should be described in detail, measured for size, and the distance from the areola should also be measured to allow for more accurate re-examination.
- If a suspicious lump is noted on examination, subsequent negative imaging should not stop further investigation.
- Simple breast cysts are often noted as discrete palpable abnormalities and will usually only need confirmation with an ultrasound; needle aspiration should be performed if the cysts are symptomatic.
- Solid masses noted on ultrasound should be biopsied to exclude cancer and obtain a histologic diagnosis.
- The diagnostic procedure of choice for most solid masses is CNB; rarely, surgical biopsy may be needed.
- Fibrocystic disease is the most common lesion in the breast and accounts for nearly 20 to 25% of all breast lesions.
- Most studies report spontaneous nipple discharge to be associated with an underlying malignancy in 5 to 10% of patients.
- Localized breast pain may be the only presenting symptom in up to 15% of women with newly diagnosed breast cancer.
- Fibroadenomas are the most common benign solid tumor of the breast and are not associated with an increased risk of breast cancer.
- Phyllodes tumors are fibroepithelial lesions that range clinically and histologically from benign to malignant.
- Phyllodes tumors are difficult to distinguish from a fibroadenoma; if a lesion does not clearly fit criteria for a fibroadenoma, then surgical excision is recommended.
- Unilateral, spontaneous bloody nipple discharge is usually caused by a benign lesion; however, histologic evaluation is required to exclude malignancy.
- Unilateral bloody nipple discharge is usually caused by an intraductal papillary lesion.
- Cytology of nipple discharge may show abnormal cells but is not useful in the management of these patients.
- The organism most commonly found in mastitis associated with breast-feeding is *S. aureus*; it may be treated with dicloxacillin, and women can continue to breast-feed while on dicloxacillin.
- Nonlactational breast abscesses are rare and are usually seen in patients who have diabetes, prolonged steroid treatment, or trauma; the most common causative organism is *S. aureus*, although mixed anaerobic organisms have also been identified.
- Breast cancer is the most common malignancy in women and the second leading cause of death from malignancy after lung cancer.
- Invasive breast cancers can be divided into two histopathologic subtypes: IDCs and invasive lobular carcinomas.
- IDCs comprise the vast majority, about 80 to 85%, of all breast cancers.
- The remaining 15 to 20% of breast cancers is composed of lobular cancers or other more rare variants.
- Through the use of gene expression profiling, breast cancers are now classified into at least four biologically distinct subtypes: luminal A, luminal B, HER2/neu overexpressing, and basal-like.
- Breast cancer is treated with surgery, radiation, and systemic (chemotherapy, hormonal, targeted) chemotherapy in varying combinations and sequences.
- Sentinel lymph node biopsy has replaced axillary lymph node dissection as a first procedure in patients with nonpalpable axillary disease.
- Different patient characteristics and tumor factors must be considered when evaluating patients for possible adjuvant therapy.
- Breast cancer is the second most common cancer encountered during pregnancy.
- Lumpectomy (segmental mastectomy) and sentinel lymph node biopsy with adjuvant radiation has the same overall survival compared to simple mastectomy and sentinel lymph node biopsy in patients with stages I and II breast cancer.
- Adjuvant systemic therapy is recommended for women with a greater than 10% chance of relapse within 10 years.
- Stage for stage, breast cancer during pregnancy has the same prognosis when matched to breast cancer patients who are not pregnant.

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CHAPTER 17

Psychiatric Disorders

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Mental health problems are common presenting and comorbid complaints in gynecologic practices.[1] In this chapter, we review the psychiatric disorders encountered most frequently in gynecologic settings, noting clinically relevant gender differences. We summarize effects of reproductive cycle events on mental health, including puberty and menarche, the perinatal period, and perimenopause. Finally, we review assessment of suicide risk, the most common psychiatric emergency encountered in gynecologic settings.

MOOD DISORDERS

Major Depressive Disorder

Major depression is the leading cause of disability in women.[2] Women experience major depression almost twice as often as men, with a lifetime prevalence of up to 25%.[3] Its predominance in women is posited to be related to genetics, the effects of hormonal flux, and gender-linked psychosocial challenges. As compared to men, women tend to have longer lasting depressive episodes, higher recurrence rates, and more comorbid anxiety and eating disorders.[4–7]

A major depressive episode is characterized by depressed mood most of the day, and/or markedly diminished interest or pleasure, for 2 weeks or more. Those mood changes are accompanied by most or all of the following symptoms: changes in sleep, changes in appetite or weight, fatigue and/or loss of energy, psychomotor agitation or slowing, feelings of worthlessness, excessive or inappropriate guilt, diminished ability to think or concentrate, indecisiveness, and recurrent thoughts of death or suicide. The differential diagnosis includes addictive substance use, medication side effects, bipolar disorder, bereavement, and medical conditions such as thyroid disease.

The diagnosis of major depression is based on the patient's reported symptoms, collateral information, and a mental status examination. When patients do not directly disclose depression, "clues" may include appearance (e.g., disheveled or disinterested), behavior (e.g., lack of direct eye contact, monotonous tone of voice), vague statements (e.g., "I haven't been myself"), or vague complaints (e.g., generally not feeling well, fatigue). Asking direct questions in an accepting manner may elicit more information.

Given the prevalence of depression, universal screening is warranted during gynecologic visits. It has been found that a single question ("Are you depressed?" or "Do you think you suffer from depression?") has adequate sensitivity and specificity as an initial screen.[8,9] Formal self-report screening tools can also be used to detect depression and to assess symptom severity and track response to treatment. The 9-item Patient Health Questionnaire (PHQ-9) is well validated in primary care settings[10] and has been used in gynecologic settings[11] (see Appendix 17.A).

Untreated episodes of major depression can last 6 to 13 months, whereas most treated episodes end within 3 months. Relapse rates are estimated at more than 50% after a single depressive episode and 80 to 90% after the second one.[12] With time, episodes tend to develop more frequently, with more intense symptoms, and without identifiable triggers. For these reasons, in cases of severe or recurrent depressive episodes, maintenance treatment may be indicated.

Antidepressant medications are recommended for moderate to severe major depressive episodes. Patients who suffer from milder depression (also referred to as subsyndromal depression) may also benefit from medication if they are not responding to other measures. Prior to initiating antidepressant medication, it is helpful to address other potential influences on depressive symptoms, such as medical conditions and medication side effects. This includes identifying and correcting nutritional deficiencies that may worsen depressive symptoms, such as iron, folate, omega-3 essential fatty acids, and vitamins B12 and D.

If the patient has a personal or family history of manic or hypomanic symptoms, it is advisable to consult with a psychiatrist *prior* to initiating treatment because antidepressants may precipitate a switch from depression to mania. Psychiatric referral is also indicated in cases where the patient is experiencing hallucinations, delusions, catatonia, or suicidal thoughts.

Antidepressant medications have comparable efficacy to one another, so the choice of a specific antidepressant

TABLE 17.1 Common Side Effects of Antidepressants and Their Management

Common Side Effects	Antidepressants With Strongest Association	Management
Weight gain	Mirtazapine, paroxetine	Nutrition consult; switch to another antidepressant.
Sedation	Mirtazapine, trazodone, TCAs except desipramine	Take at bedtime; switch to less sedating agent.
Insomnia	SSRIs, venlafaxine, bupropion, TCA except amitriptyline	Take in the morning; switch to less activating antidepressants.
Sexual side effects (decreased libido, delayed or absent orgasm)	Paroxetine	Switch to bupropion or mirtazapine.
Persistent nausea and vomiting (including exacerbation of hyperemesis gravidarum)	SSRIs, SNRIs	Take with food; switch to mirtazapine.

TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors.

is often based on side effect profiles (Table 17.1). In women, special considerations in choosing antidepressant agents include the following:

- Pregnancy, breastfeeding, or plans to conceive
- Premenstrual exacerbation of symptoms
- Comorbid disorders such as anxiety disorders, eating disorders, sleep disorders, obesity, and medical conditions that could be exacerbated by some medications
- Other symptoms that can concomitantly be alleviated by certain antidepressants. Examples include the following:
  - Serotonergic agents can alleviate premenstrual dysphoria[13] or perimenopausal vasomotor symptoms.[14]
  - Serotonin-noradrenergic reuptake inhibitors can alleviate pain, especially neuropathic pain.[15]
  - Bupropion can facilitate smoking cessation.[16]
- Side effects of particular concern to women, such as bone density reduction, weight issues, and sexual side effects

Because antidepressant pharmacokinetics can differ by sex, standard starting doses and dose ranges may be too high for some women. Women who are sensitive to initiation side effects may benefit from starting at a low dose (e.g., half the initial dose) for 4 to 5 days and then increasing at 1- to 3-week intervals as tolerated and needed. Most side effects develop within the first few days of initiation or dose increases. Many side effects are self-limiting and resolve within 2 to 3 weeks. It may take 6 to 8 weeks for an antidepressant medication to produce its maximum therapeutic effect. During this time, frequent follow-up (e.g., every 1 to 3 weeks) is indicated. If the maximum recommended dose produces no response or a partial response, psychiatric consultation should be considered for further diagnostic evaluation (e.g., assessing for contributory factors that may impede recovery) and treatment recommendations (e.g., different approaches or augmentation strategies).

It is important to educate patients about the risk of discontinuation syndrome should their antidepressant be stopped abruptly. This non–life-threatening yet uncomfortable syndrome may develop in up to 20% of patients and may include flulike symptoms, nausea, fatigue, dizziness, anxiety, and irritability.[17]

Women with mild to moderate depression may benefit from psychotherapy instead of, or in addition to, antidepressant medication. Cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) have well-demonstrated efficacy for treating major depressive disorder.[18] CBT focuses on dysfunctional thoughts and behaviors, whereas IPT focuses on improving interpersonal skills. Stress reduction, effective sleep hygiene, improved self-care, and regular physical activity can also help alleviate depressive symptoms and maintain remission.[19,20]

Seasonal Affective Disorder

Seasonal affective disorder (SAD) is a condition in which major depressive episodes occur during the fall and winter seasons and resolve in the spring. SAD is more prevalent in women than in men and often co-occurs with premenstrual dysphoric disorder.[21] Symptoms often include hypersomnia, hyperphagia with carbohydrate craving, weight gain, fatigue, and lack of energy. Before diagnosing SAD, it is important to rule out reactions to seasonally recurring stressors, such as holidays, anniversaries, or business cycles.

Phototherapy (light therapy) can be effective for SAD. Phototherapy consists of sitting 1 to 2 ft away from a therapeutic light box and glancing up at it every few seconds for 20 to 30 minutes each morning during the fall and winter months. Properly designed light boxes emit 10,000 lux of light and shield the user from ultraviolet rays. Side effects may include fatigue, irritability, insomnia, and headaches. These are usually mild and self-limiting and can be alleviated by reducing the duration of exposure. Phototherapy can induce manic symptoms in patients with bipolar diatheses.

Adjustment Disorder With Depressed Mood

Adjustment disorder with depressed mood is a short-lived, maladaptive reaction to an identifiable stressor or stressors (excluding physical illnesses, natural disasters, and bereavement). By definition, symptoms develop within 3 months of the stressor's onset and remit within 6 months of its resolution. Symptoms may include depressed mood, tearfulness, and hopelessness that cause marked distress and/or impairment in functioning. The trigger may be a common event, such as job stress, marital tension, school problems, or financial strain. The stressor's objective severity is irrelevant; symptoms

stem from the patient's personal interpretation of and adaptation to the stressors. Women are afflicted twice as often as men.[22] The treatment of choice is either individual or group psychotherapy focused on stress management.

Dysthymic Disorder

Dysthymic disorder is a chronic, low-grade form of depression with an insidious onset that lasts almost continuously for 2 years or more and impairs interpersonal and/or occupational functioning. Early onset (before age 21 years) is common. Afflicted patients may say that they have been depressed for their entire lives or that this is simply the way they are. Symptoms may include low energy, fatigue, low self-esteem, poor appetite or overeating, poor sleep or hypersomnia, hopelessness, irritability, and poor concentration. Patients tend to be pessimistic, socially withdrawn, and rarely enthusiastic about anything. The prevalence of dysthymic disorder is 6%,[23] and it is about twice as common in women as in men. Common comorbidities include major depression, anxiety, substance abuse, and personality disorders. The most effective treatment for dysthymic disorder is a combination of psychotherapy and antidepressant medication.

Depression Secondary to a General Medical Condition or Substance Abuse

Many medical conditions and substances can directly cause signs and symptoms of depression regardless of the patient's emotional response to the illness. A high index of suspicion is especially important when a depressed patient:

- Has a medical illness known to cause symptoms of depression (Table 17.2)
- Uses addictive substances or a prescribed medication known to cause depression as a side effect
- Has no personal or family history of depression
- Has depressive symptoms characterized by sudden onset or fluctuating severity
- Has symptoms and/or signs that are not part of a typical depressive disorder

Table 17.3 summarizes and compares common types of depressive disorders.

TABLE 17.2 Medical Conditions and Depressive Symptoms

Medical conditions that often present with depressive symptoms include the following:

- Endocrinologic disorders: thyroid diseases; diabetes mellitus
- Neurologic disorders: Parkinson disease, multiple sclerosis, brain tumors
- Infectious diseases affecting the central nervous system: HIV infection, herpes encephalitis
- Autoimmune diseases: systemic lupus erythematosus (SLE)

BIPOLAR DISORDER

Bipolar disorder is a chronic mood disorder characterized by recurring episodes of mania or hypomania as well as episodes of major depression. A manic episode is a period of a week or more of persistent euphoric and/or irritable mood accompanied by decreased need for sleep, grandiosity, pressured speech, racing thoughts, distractibility, increased risk taking, impulsivity, and/or increased activity. Symptoms can include delusions and/or hallucinations. Hypomanic episodes include fewer and less severe manic symptoms, with no psychotic symptoms. Patients who experience only hypomanic episodes, along with depressive episodes, have bipolar disorder type II.

As compared to men, women with bipolar disorder have[24,25] the following:

- A later onset of illness
- More seasonal patterns of mood episodes, with depressive episodes in the fall and winter months and manic episodes in the spring
- More bipolar type II
- More rapid cycling (four or more mood episodes per year)
- More frequent and lengthier depressive episodes
- More episodes of mixed depressive and manic symptoms

The mainstay of treatment for bipolar disorder is mood-stabilizing medication. Antidepressants are sometimes also used to treat and prevent depressive episodes but may trigger manic symptoms and/or rapid cycling unless a mood stabilizer is used also.[26] Treatment may also include psychotherapy and/or electroconvulsive therapy (ECT). Special considerations for women taking mood-stabilizing agents include the following:

- Studies suggest that the mood stabilizer valproate may increase the risk of polycystic ovary syndrome, although data are inconclusive.[27]
- Several mood-stabilizing agents pose risks during pregnancy. However, over 70% of women with bipolar disorder who discontinue mood-stabilizing agents while pregnant have a perinatal symptom recurrence.[28] Expert consensus guidelines[29] and specialty consultation can guide treatment plans that reduce the risks of both untreated symptoms and of medications.

ANXIETY DISORDERS

Panic Attacks and Panic Disorder

A panic attack is the sudden onset of discrete period of intense fear or discomfort, usually peaking within 10 minutes and lasting 20 to 30 minutes. During these attacks, patients experience physical symptoms, such as tachycardia, sweating, shaking, shortness of breath, chest discomfort, and feelings of light-headedness, as

TABLE 17.3 Characteristics of Depressive Disorders

Disorder	Duration	Trigger	Resolution	Preferred Treatment[a]
Major depression	At least 2 wk	Sometimes (e.g., stressful event, hormonal flux)	3 mo with treatment; 6–13 mo without treatment	Mild: psychotherapy Moderate to severe: antidepressants and/or psychotherapy
Adjustment disorder with depressed mood	Variable	Always (stressful event)	Within 6 mo of trigger's removal	Psychotherapy
Dysthymic disorder	At least 2 yr	Generally no, but stressors may worsen severity	Generally chronic without treatment	Psychotherapy with or without antidepressants
Depression due to a medical condition	At least as long as the medical problem	Underlying medical condition	Upon resolution of medical problem	Treating the underlying medical problem, antidepressants
Seasonal affective disorder (SAD)	At least 2 wk	Fall or winter; reduced sunlight	Improvement toward spring	Light therapy, antidepressants, psychotherapy

[a]Individual treatment decisions may differ based on contributory factors, patient preference, resources, and clinical judgment.

well as cognitive changes such as a fear of losing control or dying.[30]

Panic disorder exists when patients have recurrent, unexpected panic attacks. Many patients with panic disorder also have agoraphobia, or anxiety about being in public places or situations, such as crowds or public transportation, from which escape may be difficult or humiliating in the case of a panic attack.[30] Patients with panic disorder may present repeatedly to emergency rooms.

The physical symptoms characteristic of panic disorder require a workup to rule out cardiac, thyroid, parathyroid, and adrenal conditions as well as rare diagnoses such as carcinoid syndrome and pheochromocytoma. Substance-induced syndromes, such as cocaine or stimulant intoxication and alcohol withdrawal, may also mimic panic attacks.

The lifetime prevalence of panic attacks is approximately 22.7%,[31] whereas the lifetime prevalence of panic disorder is approximately 4.7%,[32] indicating that many patients with panic attacks do not develop panic disorder. Panic disorder is two to three times more common in women than in men.[33] Among patients with panic disorder, women complain more often than men of feeling faint, short of breath, or smothered.[34]

Antidepressants are effective for treating panic disorder. However, some patients with anxiety disorders, including panic disorder, experience an initial increase in anxiety upon starting antidepressants. Educating patients about this possibility, using low starting doses, and gradually increasing doses as tolerated may help patients achieve and maintain therapeutic doses. Benzodiazepines are also effective in treating panic disorder. However, given the risk for tolerance and dependence, these agents are generally best used as short-term treatment, then tapered as the antidepressant takes effect.

Psychotherapy, particularly CBT focused on relaxation techniques and cognitive restructuring, is also an effective treatment for panic disorder. Psychotherapy may be used alone or in combination with medication.[35]

Obsessive Compulsive Disorder

Obsessive compulsive disorder (OCD) is a type of anxiety disorder characterized by obsessions (persistent, intrusive thoughts) and/or compulsions (behaviors that a person feels compelled to do repetitively even though they are senseless or excessive). OCD is diagnosed when obsessions and compulsions cause marked distress and/or interfere with a person's functioning. The lifetime prevalence of OCD is somewhat higher in women than in men. The mean age of onset is later in females than in males, with the peak age of onset in females occurring during the reproductive years.[36] A subset of women appears to be vulnerable to onset or exacerbation of OCD during the luteal phase of the menstrual cycle, the perinatal period, and perimenopause.[37]

Symptom presentation can be influenced by gender and by reproductive events. Washing and cleaning rituals, fear of contamination, and aggressive obsessions are experienced more commonly by women, whereas obsessions about sex, symmetry, and exactness are experienced more often by men.[38] Aggressive obsessions about harming babies are especially frequent in postpartum OCD.[39] Mothers with nonpsychotic obsessions about harming their babies are generally horrified by these thoughts and have no desire or intent to act on them. The main risk in such cases is that the woman will avoid the baby due to her anxiety about the thoughts.

CBT is a highly effective treatment for OCD, particularly a form of CBT called exposure and response prevention. In this type of psychotherapy, patients are taught relaxation techniques and then gradually and systematically expose themselves to situations that usually trigger their compulsive behaviors. They prevent themselves from performing the compulsive behaviors while practicing techniques to manage the resultant anxiety. Serotonergic medication can also alleviate OCD symptoms.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is an anxiety disorder in which sufferers experience persistent symptoms after experiencing a highly distressing, traumatic event. The symptoms include re-experiencing the traumatic event (e.g., via nightmares or flashbacks), avoiding reminders of the event (e.g., not returning for postnatal care after a traumatic labor and delivery), and experiencing heightened arousal (e.g., difficulty sleeping, excessive startle responses). About twice as many women as men develop PTSD.[40] The median time from onset of PTSD to remission is about 1 year for men and 4 years for women.[41]

The "conditional risk" of a trauma is the likelihood that someone exposed to that trauma will develop PTSD. The traumas with the highest conditional risk—rape, sexual abuse, and intimate partner violence—are predominantly experienced by women.[42] Other traumas that predominantly affect women are difficult labor and delivery, pregnancy loss, neonatal complications, and sexual abuse of a child.

Psychotherapy is the mainstay of treatment for PTSD, particularly specific variants of CBT developed for this purpose. Antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), tricyclics, and monoamine oxidase inhibitors, can alleviate PTSD symptoms and may be useful adjuncts to psychotherapy.

Generalized Anxiety Disorder

Patients with generalized anxiety disorder (GAD) suffer from excessive, uncontrollable worry that causes marked distress and functional impairment. GAD is a chronic disorder with insidious onset and waxing and waning severity.[43] Symptoms can include pessimistic expectations, restlessness, irritability, difficulty concentrating, muscle tension, fatigue, and sleep disturbance. The focus of the patient's anxiety is not confined to just one area of concern. The lifetime prevalence is about 5 to 6%, with women being affected about twice as often as men.[44]

The GAD-7 is a validated 7-item self-administered tool that can be used to screen for GAD and to assess its severity[45] (see Appendix 17.B). The diagnostic workup also includes ruling out other potential causes of the patient's symptoms, including other mental health disorders, medical conditions, and prescribed or illicit substances.

CBT is more effective than pharmacotherapy for treating GAD.[46] When pharmacotherapy is needed, effective agents include SSRIs or serotonin–norepinephrine reuptake inhibitors (SNRIs) as first-line treatment,[47] with paroxetine, escitalopram, and venlafaxine found to be the most effective specific agents. Imipramine, buspirone, benzodiazepines, and pregabalin are second-line treatment options.[48] Other treatments that have shown some success include biofeedback[49] and the herb kava (*Piper methysticum*).[50] Results of treatment with these non–FDA-approved remedies are inconclusive, and treatment with kava has been associated with drug–drug interactions, dermopathy (with prolonged use of large amounts), and liver toxicity.[51]

EATING DISORDERS

Eating disorders have a strong predominance in women. The self-evaluation of most patients with eating disorders is strongly influenced by their weight and body shape. Specific symptoms can include binging, purging or other compensatory behavior, and/or food restriction. Binging is eating a large amount of food in a discrete period of time, with associated feelings of being out of control while eating, and feelings of shame during and after. Forms of purging include self-induced vomiting, enemas, and use of medications such as laxatives, diuretics, insulin, and ipecac. Other compensatory behaviors include compulsive overexercising and spitting out food after chewing it.

Eating disorders may arise from biological (genetics, hormones, and neurochemistry), psychological (thoughts, feelings, and beliefs), and social (cultural and interpersonal) factors. Core attitudes and symptoms of eating disorders have high heritability.[52] Social pressure to be thin is also a strong influence.

Patients often minimize or deny eating disorders, rarely reporting symptoms directly. In gynecologic practice, patients with eating disorders may present with menstrual irregularity, infertility, sexual dysfunction, low bone density, and/or fatigue.[53] Directly asking about symptoms in a nonjudgmental manner may help patients acknowledge their eating disorders. Specific areas to assess include the following[54]:

- Body image concerns
- Dieting habits
- Exercise habits
- Binging and purging
- Use of laxatives, diuretics, thyroid hormone, insulin, ipecac, stimulants, and/or enemas to lose weight
- Weight-related surgery, including gastric bypass, gastric banding, or liposuction
- Body mass index (BMI)

Gynecologist can help patients to engage in treatment for eating disorders by the following:

- Helping them focus on the misery and isolation they are suffering
- Reviewing facts about physical complications and repeating the facts if patients deny or minimize
- Letting patients know there is help

There is a significant crossover phenomenon among eating disorders. Although anorexia nervosa and bulimia nervosa are classified as distinct diagnoses, 30 to 63% of people with anorexia nervosa become bulimic at some point, and 8 to 25% of people with bulimia nervosa develop anorexia at some point.[55,56]

Anorexia Nervosa

Anorexia nervosa is a disorder that includes a refusal to maintain a minimum normal weight for age and height, related to intense fear of weight gain and becoming "fat." Patients with anorexia nervosa have a disturbance in how they experience their weight and body shape, and often deny the seriousness of their low body weight. In nonpregnant postmenarchal females who are not taking steroid hormones, the diagnosis of anorexia nervosa includes an absence of at least three consecutive menstrual cycles. There are two subtypes of anorexia. The restrictive type does not regularly engage in binging or purging behavior, whereas the binge eating/purging type regularly engages in binging and purging behaviors. Those with the restrictive type are likely to present with obsessive symptoms, a desire for perfectionism, rigid cognitive styles, and a lack of sexual interest. Those with binge eating/purging type are likely to present as impulsive and somewhat self-destructive, with higher risks for suicidal ideation.[57]

Anorexia nervosa has a lifetime prevalence of 0.5 to 3.7% in females. There is a 10% mortality rate due to starvation, suicide, and electrolyte imbalance. The most frequent age of onset is in early adolescence, but onset can occur at any age. Patients with anorexia nervosa may complain of fatigue, poor concentration, amenorrhea, loss of libido, dizziness, palpitations, coldness of the extremities, muscle weakness, or musculoskeletal pain. Appearance may be notable for overlayered clothes, relatively restricted facial expressions, lanugo bodily hair, and dull and brittle scalp hair. Electrocardiogram (ECG) may show bradycardia and/or QT prolongation.

Common psychiatric comorbidities include depression, dysthymia, OCD, other anxiety disorders, and personality disorders.[58–60] Common medical complications include malnutrition, hypothermia, muscle wasting, decreased gastrointestinal motility, and osteoporosis. Cardiac complications are frequent causes of death, often stemming from hypokalemia.

A central aspect of treatment is nutritional rehabilitation. Hospitalization should be considered in cases of the following:

- Weight loss to more than 20 to 30% below expected, and/or a BMI less than 17.5
- Symptomatic hypotension or syncope
- Heart rate 35 to 45 bpm; cardiac arrhythmias, and/or prolonged QT interval on ECG

Psychotherapy is the mainstay of treatment. Effective forms of psychotherapy include psychoeducation, motivational interviewing, and family-based treatment (FBT) (for adolescents).[61] Dialectical behavioral therapy (DBT) is a promising treatment requiring further study.[61] DBT is a combination of standard CBT and also calls on concepts of distress tolerance, acceptance, and mindful awareness. It involves individual as well as group therapy. SSRIs can be helpful for patients with comorbid depressive, obsessive, and compulsive symptoms, although patients may refuse SSRIs due to fear of weight gain. In the absence of comorbid psychiatric disorders, psychotropic medications have not been shown to be effective in decreasing relapse nor in restoring BMI.[62] Bupropion is relatively contraindicated due to increased risk for seizures.

Bulimia Nervosa

Bulimia nervosa is a disorder consisting of recurring episodes of binge eating and compensatory or purging behaviors to prevent weight gain. The binge eating and/or compensatory behaviors occur at least twice weekly for 3 months on average. Self-evaluation is excessively influenced by body weight and shape. There are two subtypes of bulimia nervosa. The purging type involves the use of self-induced vomiting or other efforts to "get rid of" calories consumed. The nonpurging type involves compensatory methods such as fasting and overexercising.

Bulimia nervosa occurs in 1 to 5% in women. Ninety percent of patients with bulimia are women. There is a high prevalence of comorbid depression, anxiety, substance abuse, and personality disorders, especially of the borderline and avoidant types.[63]

Patients with bulimia may complain of cramping, diarrhea, rectal bleeding, fatigue, difficulty concentrating, and/or irregular menses. Some patients will only report binging, purging, or other symptoms if directly asked about them. Physical signs can include dental erosion, salivary gland enlargement, and scarring of the hand (Russell sign—due to the knuckles brushing against the teeth when self-inducing vomiting). Electrolyte abnormalities may include hypokalemia, hyponatremia, elevated serum bicarbonate (due to metabolic alkalosis from vomiting), and hyperchloremia (due to metabolic acidosis from laxative abuse).

Nutritional rehabilitation is the first component of treatment. The primary goal is to reducing binge eating and purging by establishing a regular eating schedule in which the patient is eating every 3 to 4 hours instead of having long periods of restriction, which lead to urges to binge. Effective forms of psychotherapy include motivational interviewing, CBT, IPT, and DBT. Antidepressants can reduce binge eating and purging episodes while also alleviating depression, anxiety, and impulsivity. Fluoxetine is approved by the U.S. Food and Drug Administration (FDA) for this indication. Bupropion is relatively contraindicated in patients with purging due to the increased risk for seizures.

Binge Eating Disorder

Binge eating disorder consists of recurrent episodes of binge eating for at least 2 days a week over 6 months, in which at least three of the following are present:

- Eating much more rapidly than normal
- Eating until feeling uncomfortably full
- Eating large amounts of food without being hungry

- Eating alone due to being embarrassed about one's eating habits
- Feeling disgusted with oneself, depressed or guilty over eating

Binge eating disorder affects 3.5% of women and 2% of men among North American adults. Not all patients with binge eating disorder are obese, and not all patients who are obese have binge eating disorder. However, most patients with binge eating disorder are obese, with resultant complications of diabetes, high blood pressure, high cholesterol, heart disease, sleep apnea, arthritis, and stroke. Frequent comorbidities with binge eating disorder include depression, anxiety, compulsive behaviors, and substance abuse.[64]

Many patients with binge eating disorder state that they have tried every diet and still cannot lose weight or keep it off. Addressing emotional eating patterns may improve outcome. Behavioral weight loss is less effective than motivational interviewing, IPT, and CBT.[65] DBT is a promising treatment that is being studied.[66]

Antidepressants can be effective adjuncts to treatment, with the caveat that several antidepressants can cause weight gain as a side effect. Another option is the FDA-approved antiobesity agent sibutramine. Although naltrexone and topiramate have been used to decrease binge eating, neither is FDA-approved for this indication.

ADDICTIVE DISORDERS

Substance use disorders are highly prevalent chronic illnesses, in which relapses are common and long-term care strategies are critical in producing good outcomes.[67] Historically, substance use disorders in women have been under-recognized.[68] Although the prevalence is higher in men, over the last few decades, increasing numbers of women have been identified as having substance use disorders.[49,69-71] Large national surveys have found that the lifetime prevalence of alcohol use disorders is 19.5% of women and 42.0% in men,[70] whereas the 12-month prevalence for drug use disorder is 6.2% in women and 9.9% in men.[71] The gender differential is reduced in participants aged 12 to 17 years.[71] There is a higher prevalence of depression, anxiety, eating disorder, and PTSD in substance-using women as compared to men.[72,73]

A striking gender difference in the clinical course of substance use disorders, particularly alcohol, is the "telescoping" effect, where the progress from first use to treatment seeking tends to be shorter for women than men.[74] A possible explanation is that women may be more susceptible to the medical and psychiatric consequences of substance use.[75] For example, women become more intoxicated and experience higher serum alcohol concentrations than men. Women also develop liver disease as well as die from liver cirrhosis after consuming less alcohol and for a shorter duration than men.[76] Women cigarette smokers may be more at risk for lung cancer than men and are more likely to contract HIV from intravenous drug use.[77]

TABLE 17.4 Safe Drinking Limits for Women

	Recommended Weekly Limit	Recommended Daily Limit
For women who are in good general health	Not more than seven drinks[a] in a week	Not more than three drinks[a] in a day
For women who: • **Meet criteria for an alcohol use disorder** • **Take medications that can interact with alcohol (i.e., warfarin)** • **Are pregnant** • **Are medically ill**	Recommend abstinence from all alcoholic beverages	Recommend abstinence from all alcoholic beverages

[a]One drink = 12 oz of beer or 5 oz of wine or 1.5 oz of liquor.
From National Institute of Alcohol Abuse and Alcoholism. *Helping Patients Who Drink Too Much: A Clinician's Guide*. Rockville, MD: National Institute of Alcohol Abuse and Alcoholism. NIH publication 05-3769, Revised.

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines (Table 17.4) recommend that women consume no more than seven drinks per week on average and no more than three drinks in 1 day, and less if there are conditions that make this amount of drinking hazardous.[78] A pattern of drinking above these limits is considered to be at-risk drinking. For tobacco and other addictive drugs (e.g., heroin, cocaine, cannabis), any use is considered to be at-risk use.

There are two categories of substance use disorders: substance abuse and substance dependence (i.e., addiction). Substance dependence is diagnosed when a woman engages in repeated and intensive use of the substance that she cannot control, develops physiologic dependence (i.e., tolerance and withdrawal), and continues use despite knowing the harm being caused. Substance abuse is diagnosed when a woman either repeatedly engages in the use of that substance in hazardous situations (e.g., driving), or the substance use leads to repeated failures in meeting role obligations (e.g., calling in sick to work), social conflicts (e.g., arguments with spouse), or legal problems (e.g., arrests for driving while intoxicated).

Assessment begins with screening questions for alcohol, tobacco, and drug use (Table 17.5). A nonjudgmental and empathic approach is important because patients may be reluctant to disclose addictive substance use due to embarrassment, shame, and/or fear of legal repercussions. For those who screen positive, assessing the following can help determine diagnosis and patterns of use[81]:

- Frequency and quantity of use
- First and most recent use
- Longest period of sobriety
- Routes of ingestion

TABLE 17.5 Screening Questions for Addictive Substance Use

NIAAA questions for alcohol[78]	1. On average, how many days a week do you have an alcoholic drink? 2. On a typical drinking day, how many drinks do you have? 3. How many times in the past year have you had four or more drinks in a day?
CAGE for alcohol and/or drugs[79,80]	C—Have you felt the need to Cut down your drinking (or drug use)? A—Have people Annoyed you by criticizing your drinking (or drug use)? G—Have you felt Guilty about your drinking (or drug use)? E—Have you ever had a drink (or used drugs) first thing in the morning to steady your nerves or get rid of a hangover (Eye-opener)?

NIAAA, National Institute on Alcohol Abuse and Alcoholism; CAGE, cut down, annoyed, guilty, eye-opener.

- History of withdrawal
- Prior engagement with treatment, including self-help groups
- History of substance-related legal issues
- Interference with work and/or social role obligations
- Harmful effects on physical or psychological health
- Use in hazardous situations

Relevant laboratory tests include blood alcohol level, urine toxicology screens, and liver function tests, specifically aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyl transferase (GGT). Most urine opiate screens are calibrated to morphine, with poor sensitivity for semisynthetic opiates such as oxycodone and hydrocodone, and virtually no sensitivity for synthetic opioids such as methadone or fentanyl.[82]

Individuals who screen positive should be offered a brief intervention. Those who meet criteria for a substance use disorder should also be referred for further addiction treatment. Patients who may have overdosed or who are acutely withdrawing may need to be sent to an emergency room or inpatient detoxification service.

"Brief intervention" typically refers to single-session interventions that last less than 30 minutes. Even physician interventions lasting 5 minutes can have an impact on future substance use.[83] Motivational interviewing is a particular communication style that has been adapted for use as a brief intervention for numerous health behaviors. It consists of asking permission to discuss the topic, exploring the patient's motivations for change, avoiding confronting or arguing, and listening with empathy.[84] If the patient is ready to change her behavior, the clinician and the patient can collaboratively negotiate a plan. If the patient does not feel ready to make changes, the clinician can acknowledge the patient's willingness to talk about a difficult subject and reaffirm the commitment to helping the patient. For patients with substance use disorders, the central goal of brief intervention is to refer patients to addiction treatment. Men and women have comparable treatment outcomes, although some studies indicate that gender-specific treatment programs may produce better outcomes.[85] For women with comorbid psychiatric illnesses, an integrated treatment approach is critical, because otherwise untreated psychiatric symptoms can trigger addictive substance use, and ongoing substance use can interfere with recovery from other psychiatric disorders.

For alcohol, opioids, and tobacco, medications as a longer term maintenance treatment (as summarized in Table 17.6) may play a role in the recovery process. At this time, no medications have been FDA approved for the treatment of cocaine, stimulants, sedative/hypnotics, hallucinogens, or dissociatives.

REPRODUCTIVE-LINKED PSYCHIATRIC DISORDERS

Psychiatric Disorders at Puberty and Menarche

At midpuberty, the prevalence of depression, panic disorder, OCD, and eating disorders becomes substantially higher in girls as compared to boys.[86,87] The risk of depression and panic disorder in girls correlates with stage of puberty rather than with chronological age[88,89] and is more pronounced in girls with earlier onset of puberty.[90] Hormonal flux is posited to contribute to risk of depression around the onset of menarche. In addition, certain psychosocial stressors strongly influence the risk of depression in teenaged girls, most notably, sexual abuse.[91] Styles of reacting to stress also play a key role. On average, more girls than boys tend to believe that adverse events are their fault and tend to ruminate about them, whereas more boys than girls use active problem-solving approaches.[92] A problem-solving stance confers more protection against depression than a ruminative stance.

When evaluating adolescent girls who have depressive symptoms, asking about specific contributory factors can guide effective interventions. Table 17.7 summarizes risk factors and targeted nonpharmacologic treatment approaches.

Decisions about whether to prescribe antidepressant medication to adolescent girls require careful risk–benefit analyses. Among antidepressants, only fluoxetine has demonstrable efficacy for adolescent depression.[93] An FDA black box warning underscores an increased risk of suicide in adolescents from antidepressant use,[94] although successful treatment of depression can prevent suicide. Antidepressant side effects that especially troublesome adolescent girls include weight gain, sexual dysfunction, and sleep disruption. The Treatment of Adolescent Depression Study[95] found that short-term effectiveness was best for combined CBT and fluoxetine, next best for fluoxetine alone, and least for CBT alone. However, long-term efficacy was similar for all three.

TABLE 17.6 Medications for Addiction Treatment

Substance	Medication	Mechanism	Contraindications	Side Effects	Dosage
Alcohol	Naltrexone	Opioid antagonist	Currently on opioids; liver disease	Precipitated withdrawal in those on opioids; nausea, vomiting, headache, dizziness, fatigue	50 mg orally daily
	Acamprosate	Glutamate modulator	Severe renal impairment	Nausea, diarrhea, somnolence	666 mg orally, three times daily
	Disulfiram	Inhibits aldehyde dehydrogenase	Concomitant use of alcohol	Flushing reaction if alcohol used; hepatotoxicity; optic neuritis, psychosis	500 mg orally daily
Opioid	Buprenorphine	Partial opioid agonist	Currently on opioids; use caution in those with history of hepatitis C	Precipitated withdrawal in those on opioids; headache, sweating, constipation	Varies (2–32 mg daily or divided)
	Methadone	Opioid agonist	Numerous drug–drug interactions	Headache, sweating, constipation, QT prolongation	Varies (target >80 mg daily)
Tobacco	Bupropion	Dopamine and norepinephrine reuptake inhibitor	Seizure disorder, eating disorder, MAO inhibitors	Insomnia, dry mouth, anxiety, seizures, suicidality (rare)	150 mg orally daily for 3 d, then twice daily
	Nicotine replacement	Nicotinic receptor agonist	Use caution in those with serious cardiac disease	Vivid dreams; skin reactions (patch); nausea, hiccup, heartburn (gum); nasal irritation (inhaler)	Varies
	Varenicline	Nicotinic receptor partial agonist	Use caution in those with history of psychiatric illness or severe renal impairment	Black box warning for neuropsychiatric symptoms and suicidality	0.5 mg orally daily for 3 d, then twice daily for 4 d, then 1 mg orally twice daily

MAO, monoamine oxidase.

Recommendations for treating pubertal-onset depression in girls include the following:

- Initiate psychotherapy focused on specific risk factors.
- Add fluoxetine if depressive symptoms are severe and substantially interfering with functioning, and/or if symptoms are not remitting with psychotherapy.
- Monitor for medication side effects and resultant effects on body image (weight gain), school performance and driving safety (sedation), and self-esteem (stigma of mental illness and its treatment).
- Monitor closely for suicide risk.

TABLE 17.7 Assessing and Treating Depression in Adolescent Girls

Contributory Factors	Therapeutic Interventions
Ruminative cognitive style	• Cognitive behavioral therapy (CBT) focused on problem solving and stress management
History of sexual abuse	• Safety measures as needed • Psychotherapy focused on recovery from sexual trauma
Body dissatisfaction	• Psychotherapy focused on improving self-esteem and body image
Peer pressure	• Interpersonal psychotherapy • Assertiveness training
Family conflicts	• Family therapy • Interpersonal psychotherapy

Perinatal Depression

Between 14 and 23% of pregnant women will experience a depressive episode while pregnant.[96] Antenatal maternal depression can increase the risk of preterm delivery[97] and neonatal irritability.[98] Newborns of depressed mothers have elevated cortisol compared to newborns of nondepressed mothers and may have reduced stress tolerance later in life.[99]

As many as 19.2% of women giving birth develop an episode of major depression within the first 3 months postpartum.[100] Women who have experienced prior episodes of postpartum depression[101] or depressive symptoms while pregnant[102] are at heightened risk for developing postpartum depression.

Postpartum "blues" are normal mood changes experienced by about 50% of women following delivery.[103] Postpartum blues consists of reactivity of mood, tearfulness, and irritability that usually begin about 3 to 5 days postpartum and remit within days to weeks.[104] Most women with postpartum blues do not experience sadness or emptiness as their predominant mood state; rather, they feel happy or normal most of the time but have frequently changing moods. When sadness predominates and/or when symptoms persist beyond a few weeks, the "blues" may evolve into a depressive episode.[102]

Postpartum depression (formally diagnosed as major depression with postpartum onset) may be difficult to recognize because the symptoms may be mistaken for "blues" or other normal postpartum changes. The key

difference is the persistence of sadness, emptiness, and/or lack of joy, along with other symptoms of major depression. Women with postpartum depression may also experience obsessional thoughts, which are often aggressive in nature and may include thoughts about harming their babies. These thoughts are similar to the thoughts that occur to some women with postpartum OCD. They are not associated with increased risk of harming babies unless other risk factors are present, such as psychosis, impulsiveness, and a history of violence. Nevertheless, untreated postpartum depression can adversely affect a child's development and well-being[105] and can be stressful for all family members.[106]

Postpartum psychosis occurs in 0.2% of women of childbearing age.[107] Women with this disorder may experience hallucinations, delusions, unusual behavior, agitation, disorganized thoughts, and inability to sleep. Often, the hallucinations and delusions center on the baby. In rare cases, the psychotic symptoms may include hallucinated voices commanding a woman to harm her baby and/or delusions that cause a woman to harm her baby (e.g., a belief that the baby is a demon). In such cases, prompt intervention may be vital to protect both mother and child.[108]

Using self-report questionnaires has been found to be far more effective for detecting perinatal depression than routine clinical detection. However, some depression screening tools can be misleading because some of the symptoms of depression are found in nondepressed pregnant women (e.g., fatigue, changes in sleep and appetite). The most well-validated screening questionnaire for depression during pregnancy and postpartum is the Edinburgh Postnatal Depression Scale.[109] For women who are pregnant and have a history of depression, the Pregnancy Depression Scale (PDS) may also be used.[109a]

Treatments with demonstrated efficacy for perinatal depression include IPT,[110] CBT,[111] ECT,[112] and antidepressant medication.[113] IPT promotes effective elicitation of social support and adjustment to motherhood. CBT can focus on problem solving and realistic expectations about motherhood. ECT can relatively rapidly alleviate severe perinatal depression that poses immanent risks (e.g., suicidal intent). Its technique can be modified during pregnancy to minimize risks to mother and fetus. Other promising interventions needing further study include estradiol,[114] phototherapy,[115] and omega-3 essential fatty acids.[116]

Weighing the risks and benefits of using antidepressant medication during pregnancy or postpartum is challenging but essential. General guidelines for prescribing antidepressants during pregnancy include the following:

- Assess whether nonpharmacologic treatment is feasible and will be sufficiently effective.
- Choose a medication regimen that is effective. A common error is to use a subtherapeutic dose in the mistaken belief that this will reduce risks to a fetus. Instead, it may expose the fetus to both the risks of the untreated depressive symptoms and the risks of the medication.
- Understand the meaning and limitations of FDA Pregnancy Risk categories. A common error is to think that Category B is "safer" than Category C, which is in turn "safer" than Category D. However, animal studies substantially influence this categorization, and the findings from those studies do not generalize to humans. It is prudent to base clinical decisions on findings from systematic studies in humans, particularly prospective, controlled studies and meta-analyses.
- Pharmacokinetics changes during pregnancy, such that some women need higher antidepressant doses to achieve a therapeutic effect.

General guidelines for prescribing antidepressants postpartum include the following:

- Pay close attention to sedative side effects. Daytime sedation may reduce energy to parent. Excessive nighttime sedation may lead to difficulty awakening to care for a baby and can, in some instances, lead to a mother dropping her baby.
- Avoid medications that contribute to insomnia, which may add to the sleep deprivation already experienced by most new mothers.
- Discuss with patients their attitudes about possible side effects of weight gain and sexual dysfunction. Some women find these side effects to be especially problematic postpartum because they may prioritize losing pregnancy weight and resuming sexual relations.

Additional issues arise for women who are breast-feeding. Despite its benefits, some women find breast-feeding more stressful than relaxing. Compared to nondepressed mothers, mothers with postpartum depression breast-feed less.[117] Women with postpartum depression may face a decision about whether to take antidepressant medication while breast-feeding and/or whether to stop breast-feeding. Gynecologists can help by informing patients about the effects of untreated postpartum depression, the effects of antidepressant exposure on breast-feeding babies, and options in cases where breast-feeding is stressful. Such options can range from breast-feeding support (e.g., a lactation consultant) to partial bottle-feeding to weaning. Communicating with the baby's pediatrician can improve the chances that the patient will receive consistent information and can coordinate monitoring of maternal and infant health.

Overall, the exposure of infants to antidepressants through breast milk is relatively low.[118] The antidepressants most recommended during breast-feeding are sertraline, paroxetine, nortriptyline, and imipramine due to a comparatively larger body of data showing low infant

exposure, trace to undetectable infant serum levels, and no reports of short-term adverse events (see Appendix 17.C).

Gynecologists can play a major role in promoting better pregnancy outcomes for women with depressive disorders by encouraging preconception planning. Patients who have had a single episode of depression and have been free of symptoms for 6 months or longer may be candidates for medication taper and discontinuation prior to conception. When discontinuing medication, psychotherapy may help a woman identify potential triggers for future episodes and practice strategies to manage anticipated stressors. Patients with a history of severe, recurrent major depression, and/or a history of psychosis or suicide attempts, may not be candidates for medication discontinuation.

Infertility

Psychiatric disorders are significantly more prevalent in women who are undergoing infertility treatment than in fertile women.[119] What remains unclear is whether certain types of psychopathology reduce fertility or whether most of the increase in psychopathology arises as a consequence of infertility and its treatment. Key influences on risk for depression and anxiety include the following:

- A feeling of loss of control over one's life, often including substantial lifestyle adjustments due to the scheduling demands of infertility treatment
- Focusing on infertility to the exclusion of other important aspects of life
- Sex feeling mechanized, with diminished emotional intimacy[120]
- Personal and interpersonal tension about the profound moral implications of decisions about reproductive technologies and risks
- Strained relationships with relatives and friends, including some who are having babies and some who are perceived as pressuring a couple to conceive[121]
- Mood effects of hormones used to treat infertility, although depression appears to be a rare side effect of infertility medications[122]

Gynecologists can help women undergoing infertility treatment to maintain their emotional equilibrium in several ways[121]:

- Helping patients develop a realistic understanding of the physical and emotional risks of infertility procedures and of prognosis
- Helping patients think through their own values, resources, and options
- Facilitating communication between members of the couple and their family members and friends
- Identifying and treating psychiatric disorders which occur before, during, or after assisted reproduction

Individual or group psychotherapy encompassing relaxation techniques, stress management, and coping skills training can reduce depressive and anxiety symptoms during infertility treatment.[123] For more severe symptoms that are not responsive to psychotherapy, antidepressant medication may be indicated.

Pregnancy Loss

Miscarriage

Psychological reactions to miscarriage are variable and individualized. Frequent normal reactions include grief, sadness, anger, anxiety, guilt, preoccupation with the loss, and a search for the meaning of the loss. Miscarriage can also precipitate more severe psychiatric reactions, including major depressive episodes and PTSD. Risk factors for PTSD after miscarriage include greater perceived threat, more prior negative life events, and greater exposure to blood and tissue during the miscarriage. Protective factors include strong social support and ability to express feelings.[124] The main risk factor for developing major depression after miscarriage is a prior history of depression.[125]

Gynecologists can play a key role in early detection and prevention of psychiatric complications of miscarriage by the following[126]:

- Scheduling a follow-up appointment within a week of the miscarriage to discuss the patient's reactions.
- Explaining the range and depth of normal grief reactions.
- Asking about social support. Even women who have strong support networks may feel isolated while grieving a miscarriage if they come from cultures that do not foster grieving for a miscarriage.
- Asking about the partner's reactions. Compared to women as a group, men have been found to talk less about their reactions to miscarriage and to resume their usual routines more quickly.[127] Helping partners to recognize and respect one another's coping styles can reduce interpersonal tension.[128]
- Consider referral to a perinatal loss group, and if substantial distress persists 2 months after the miscarriage, consider referral to a mental health professional.
- Advise patients to treat psychiatric sequelae of miscarriage before trying to conceive another pregnancy because unresolved symptoms can intensify during a subsequent pregnancy.

Elective Abortion

For women who choose to abort a pregnancy, anxiety and depressive symptoms are most pronounced after learning of the pregnancy and before having the procedure.[129] After an abortion, normal reactions may include sadness, anxiety, regret, guilt, and relief.[129,130] The best predictor of more serious mental health problems after abortion is pre-existing mental health problems, which in turn are correlated with a history of sexual

abuse and/or intimate violence.[131] Other predictors of postabortion depressive symptoms are doubts about the decision, negative attitudes toward elective abortion,[132] and late-pregnancy abortion of a wanted fetus due to fetal anomaly.[133] Preabortion counseling can help alleviate psychological distress by the following:

- Helping a woman arrive at a decision about abortion without feeling pressured or stigmatized and with information about the risks of abortion and the risks of pregnancy
- Identifying and treating pre-existing psychiatric problems and psychosocial stressors

Stillbirth

For many women, stillbirth is a uniquely painful type of loss. It is usually unexpected and often traumatic. There is no opportunity to accrue a sense of the baby as an individual or to accumulate memories. In some cultures, there is little recognition of the meaning or intensity of the loss and little understanding of how to talk about the loss, such that grieving parents feel isolated. Members of a couple may have different styles of grieving, such that the coping strategies of one (e.g., talking about the loss, viewing pictures, keeping mementos) may clash with those of the other (e.g., focusing on other activities as a distraction).

Experiencing a stillbirth confers a high risk of depression[134] and PTSD.[135] The risk of PTSD after stillbirth is greater in women who feel insufficiently emotionally supported by their partners or family members.[135] Symptoms of both depression and PTSD intensify in many women during a subsequent pregnancy, usually resolving postpartum after the birth of a healthy baby.[134,135] In a few cases, symptoms of either depression or PTSD become chronic.

Many bereaved mothers wish to hold their stillborn babies so that they can form specific memories of the baby. However, in some women, this increases the risk of PTSD.[136] This underscores that grieving is a highly individualized process and that there is no one style of "healthy" grieving. Gynecologists can help by supporting a woman's own grieving style and by encouraging patients to gradually resume normal activities, even when that involves emotionally painful exposure to other babies or pregnant women.

Women who have experienced stillbirth may ask gynecologists about optimal timing of a subsequent pregnancy. Data show that the risk of depression during a subsequent pregnancy is increased if a woman conceives within a year after a stillbirth as compared to waiting longer.[134] However, individual circumstances may influence optimal timing for each woman.

Perimenopausal Depression

The transition to menopause is a time of heightened risk for depression. As compared to pre- and postmenopause, women undergoing perimenopause have approximately twice the risk of experiencing a major depressive episode[137] and about four times the risk of experiencing subsyndromal depressive symptoms.[138] Absolute levels of sex hormones do not correlate with having depressive symptoms. However, consistent with the hypothesis that hormonal flux increases vulnerability to depression in some women, increased variability of estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) around a woman's mean levels is associated with a greater likelihood of having depressive symptoms.[138]

Stress is another major influence on whether a woman becomes depressed during perimenopause. Heart rate, blood pressure, and epinephrine responses to stress are greater in perimenopausal than in premenopausal women.[139] Frequent stressors for women at midlife include the following:

- Marital/significant other tensions: This may occur when partners within a couple have different and conflicting aspirations at midlife.
- Parenting/family tensions: In many families, perimenopause in a mother coincides with adolescence in children, with heightened tensions related to a combination of hormonal flux and social role changes in both generations. Perimenopause may also coincide with a woman becoming more of a caregiver for aging parents.
- Career/social role stress: Women in certain social contexts find themselves less valued as they age.
- Losses: For some women, midlife is a time when people close to them are dying or developing serious illness. In addition, women may experience the onset of chronic medical illnesses that limit their functioning and change their self-image.

Effective treatment of perimenopausal depressive symptoms can include psychotherapy, antidepressant medication, estrogen, and aerobic exercise. Table 17.8 summarizes antidepressant side effects that are especially relevant when deciding whether to prescribe medication, or which medication to prescribe, for a depressed perimenopausal woman. Because women

TABLE 17.8 Antidepressant Side Effects With Particular Relevance to Perimenopausal Women

Antidepressant Side Effect	Medications Most Associated
Reduced bone density	Selective serotonin reuptake inhibitors (SSRIs)
Weight gain	Clomipramine, mirtazapine, paroxetine
Sedation	Mirtazapine, amitriptyline, trazodone
Insomnia	SSRIs, venlafaxine
Sexual dysfunction	Paroxetine and other SSRIs
Hypertension	Serotonin–norepinephrine reuptake inhibitors (SNRIs)

with depressive symptoms are almost twice as likely to have hot flashes as are perimenopausal women without depression,[140] it may be helpful to choose an antidepressant known to alleviate vasomotor symptoms. These include paroxetine, fluoxetine, citalopram, venlafaxine, and desvenlafaxine.[141] Less commonly, hot flashes can be a side effect of antidepressant use.

Estradiol alleviates depressive symptoms better than placebo[141] but does not reliably treat major depressive episodes as monotherapy. It is not FDA approved for use as an antidepressant but may alleviate subsyndromal depression in women with other indications for use. It may augment response in some perimenopausal women who have a partial response to antidepressant medication.[142]

Among nonpharmacologic treatments, IPT is especially relevant for women who are modifying social roles that are no longer a good fit, trying out new roles, and negotiating with others to change unhelpful interpersonal patterns. Aerobic exercise alleviates depressive symptoms while also reducing hot flashes, improving sleep, maintaining bone density and muscle mass, and reducing neurophysiologic damage from stress. Despite these health benefits, physical activity declines in many women after menopause.[143] Clinicians can promote physical activity in their patients by the following:

- Prescribing it explicitly as part of their treatment
- Recommending a safe, realistic exercise regimen while allaying unfounded fears about adverse effects of exercise. This can include cumulative activity (e.g., several brief walks) that is incorporated into everyday life.
- Encouraging a woman to have the goal of increased well-being, rather than weight loss[144]

Many women are attracted to the idea of using herbal remedies for perimenopausal depression. Treatment with complementary and alternative medical therapies is discussed in a separate chapter.

SUICIDE

Women are three times more likely than men to attempt suicide but account for only 35% of completed suicides.[145,146] Women are more likely to reveal suicidal ideation prior to their attempts.[145] The most effective way to screen for suicidal thoughts is to ask about them directly. Asking in a nonjudgmental way will not suggest new ideas to a suffering patient. Rather, patients are likely to feel relieved to discuss frightening thoughts. If a woman acknowledges suicidal thoughts, the level of risk can be ascertained by assessing for the following:

- Specific plans (e.g., "Did you think about how you would do it?")
- Means (e.g., "Do you have access to guns/medicine/high buildings?")
- Intent (e.g., "Do you think you would do it? What steps have you taken toward acting on your plan?")

Indications for emergency evaluation include the following:

- The patient confirms her intent to attempt suicide.
- The patient seems ambivalent but has gradually come closer to carrying out a plan.
- Clinician uncertainty about the seriousness of the suicidality

CONCLUSION

There is a high prevalence of mood disorders, anxiety disorders, eating disorders, and addictive disorders among women seen in gynecologic practice. Understanding the influence of gender and reproductive cycle events on these disorders can inform diagnosis and treatment planning. Detecting and treating these disorders can profoundly influence the physical and mental health of the women who suffer from them.

CLINICAL NOTES

- Major depression is the leading cause of disability in women.
- Women experience major depression almost twice as often as men, with a lifetime prevalence of up to 25%.
- A major depressive episode is characterized by depressed mood most of the day, and/or markedly diminished interest or pleasure, for 2 weeks or more.
- Untreated episodes of major depression can last 6 to 13 months, whereas most treated episodes end within 3 months. Relapse rates are estimated at more than 50% after a single depressive episode and 80 to 90% after the second one.
- Antidepressant medications are recommended for moderate to severe major depressive episodes.
- If the patient has a personal or family history of manic or hypomanic symptoms, it is advisable to consult with a psychiatrist *prior* to initiating treatment because antidepressants may precipitate a switch from depression to mania.
- Antidepressant medications have comparable efficacy to one another, so the choice of a specific antidepressant is often based on side effect profiles.
- Patients should be told about the risk of discontinuation syndrome should their antidepressant be stopped abruptly because this non–life-threatening yet uncomfortable syndrome may develop in up to 20% of patients and may include flulike symptoms, nausea, fatigue, dizziness, anxiety, and irritability.

(continues)

- Women with mild to moderate depression may benefit from psychotherapy instead of, or in addition to, antidepressant medication.
- Adjustment disorder with depressed mood is a short-lived, maladaptive reaction to an identifiable stressor or stressors; by definition, symptoms develop within 3 months of the stressor's onset and remit within 6 months of its resolution.
- Dysthymic disorder is a chronic, low-grade form of depression with an insidious onset that lasts almost continuously for 2 years or more and impairs interpersonal and/or occupational functioning. Early onset (before age 21 years) is common.
- Many medical conditions and substances can directly cause signs and symptoms of depression regardless of the patient's emotional response to the illness.
- Bipolar disorder is a chronic mood disorder characterized by recurring episodes of mania or hypomania as well as episodes of major depression.
- The mainstay of treatment for bipolar disorder is mood-stabilizing medication.
- Several mood-stabilizing agents pose risks during pregnancy. However, over 70% of women with bipolar disorder who discontinue mood-stabilizing agents while pregnant have a perinatal symptom recurrence.
- The lifetime prevalence of panic attacks is approximately 22.7%, whereas the lifetime prevalence of panic disorder is approximately 4.7%, indicating that many patients with panic attacks do not develop panic disorder.
- Antidepressants are effective for treating panic disorder, although some patients may experience an initial increase in anxiety upon starting antidepressants.
- Psychotherapy, particularly CBT focused on relaxation techniques and cognitive restructuring, is an effective treatment for panic disorder.
- OCD is diagnosed when obsessions and compulsions cause marked distress and/or interfere with a person's functioning. Aggressive obsessions about harming babies are especially frequent in postpartum OCD.
- CBT is a highly effective psychological treatment for OCD, particularly a form of CBT called exposure and response prevention.
- PTSD is an anxiety disorder in which sufferers experience persistent symptoms after experiencing a highly distressing, traumatic event. About twice as many women as men develop PTSD and the median time from onset of PTSD to remission is about 1 year for men and 4 years for women.
- Psychotherapy is the mainstay of treatment for PTSD, particularly specific variants of CBT developed for this purpose.
- Patients with GAD suffer from excessive, uncontrollable worry that causes marked distress and functional impairment; CBT is more effective than pharmacotherapy for treating GAD.
- There is a significant crossover phenomenon among eating disorders. Although anorexia nervosa and bulimia nervosa are classified as distinct diagnoses, 30 to 63% of people with anorexia nervosa become bulimic at some point, and 8 to 25% of people with bulimia nervosa develop anorexia at some point.
- The lifetime prevalence of alcohol use disorders is 19.5% of women and 42.0% in men, whereas the 12-month prevalence for drug use disorder is 6.2% in women and 9.9% in men.
- There are two categories of substance use disorders: substance abuse and substance dependence (i.e., addiction).
- At midpuberty, the prevalence of depression, panic disorder, OCD, and eating disorders becomes substantially higher in girls as compared to boys. The risk of depression and panic disorder in girls correlates with stage of puberty rather than with chronological age and is more pronounced in girls with earlier onset of puberty.
- Between 14 and 23% of pregnant women will experience a depressive episode while pregnant.
- Postpartum "blues" are normal mood changes experienced by about 50% of women following delivery. Postpartum depression may be difficult to recognize because the symptoms may be mistaken for "blues" or other normal postpartum changes, but the key difference lies in the persistence of anhedonia or sadness, along with other symptoms of major depression.
- Postpartum psychosis occurs in 0.2% of women of childbearing age.
- The transition to menopause is a time of heightened risk for depression with women undergoing perimenopause, having approximately twice the risk of experiencing a major depressive episode and about four times the risk of experiencing subsyndromal depressive symptoms.
- Women are three times more likely than men to attempt suicide but account for only 35% of completed suicides and are more likely to reveal suicidal ideation prior to their attempts.
- The most effective way to screen for suicidal thoughts is to ask about them directly. Asking in a nonjudgmental way will not suggest new ideas to a suffering patient.

Appendix 17.A

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last *2 weeks,* how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+
		TOTAL:		

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

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PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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Appendix 17.B

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Inern Med.* 2006;166:1092-1097.

Scores of 5, 10, and 15 are taken as the cutoff points for mild, moderate, and severe anxiety, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater.

Appendix 17.C
Lactation Risk Categories

L1 SAFEST:
Drug which has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote; or the product is not orally bioavailable in an infant.

L2 SAFER:
Drug which has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant; and/or, the evidence of a demonstrated risk which is likely to follow use of this medication in a breastfeeding woman is remote.

L3 MODERATELY SAFE:
There are no controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible; or, controlled studies show only minimal nonthreatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant.

L4 POSSIBLY HAZARDOUS:
There is positive evidence of risk to a breastfed infant or to breast milk production, but the benefits of use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

L5 CONTRAINDICATED:
Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

This rating system is based on the amount of study data available for a specific medication; new or seldom-used drugs have usually not been well studied. Another estimate of risk is determined by the level of exposure for an infant who is nursing. This is often reported as the Relative Infant Dose (RID). It is expressed as a percentage and is calculated by dividing the infant's total daily ingestion of a drug via nursing (mg/kg of infant body weight) by the mother's daily dose (mg/kg maternal body weight). While many consider an RID $<10\%$ to be safe, this is an empirical judgment.

From Hale TW. *Medications and Mothers' Milk: A Manual of Lactational Pharmacology*. 11th ed. Amarillo, TX: Pharmasoft Medical Publishing; 2004.

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CHAPTER 18

Intimate Partner Violence

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Intimate partner violence (IPV) is a pattern of coercive behaviors that may include repeated sexual and physical violence, psychological abuse, reproductive coercion, and stalking and often results in progressive social isolation, deprivation, and intimidation of the victim. These behaviors are perpetrated by someone who is or was involved in an intimate relationship with the victim and are used to establish power and control over the victim.[1,2] IPV can occur among heterosexual or same-sex couples and does not require sexual intimacy to be present, either currently or in the past, to occur. IPV is estimated to result in 2 million injuries to women and nearly 600,000 injuries to men on an annual basis.[3] The assumption that all IPV is initiated by men and directed toward women in heterosexual relationships is not correct, although women are far more likely to experience IPV than men.[4]

IPV cuts across gender, racial, ethnic, and socioeconomic boundaries, although certain groups are at greater risk for either suffering from or perpetrating IPV.[5] Accurate prevalence figures for IPV are difficult to get because of underreporting and differences in IPV definitions and data collection methods. Lifetime estimates for IPV involving women in the United States range from 22 to 39%.[3,6] The prevalence of IPV involving male victims is not well known, although a 2010 national survey found that about one in four men had experienced rape, physical violence, and/or stalking by an intimate partner at least once in their lifetime.[2]

Most IPV physical assaults are relatively minor and consist of pushing, grabbing, shoving, slapping, and hitting.[7] However, IPV resulted in an estimated 2340 deaths in 2007, with 70% occurring in women and 30% in men.[3] Murder by a partner is among the five most common causes of death for women ages 15 to 34 years.[8] In many cases, there are historical indicators of escalating levels of violence. In one study, 44% of women murdered by their intimate partner had been to an emergency department within 2 years of the homicide, and 93% had at least one injury visit.[9]

According to the World Health Organization, two patterns of violence between couples have been described.[4] "Battering" involves severe and escalating violence with concurrent terrorization and increasingly controlling behavior by the abuser. "Common couple violence" is a more moderate form of IPV in which violence occurs occasionally and is usually triggered by frustration and/or anger. IPV is often categorized into four main types: physical violence, sexual violence, psychological/emotional violence, and stalking.[10] Experiencing one type of IPV-related abuse may increase the risk of other types of abuse. In one study, 68% of physically abused women were also sexually abused.[11]

Physical violence is the intentional use of physical force with the potential for causing death, disability, injury, or harm. Physical violence includes, but is not limited to, such things as scratching, shoving, biting, choking, shaking, and slapping punch. It may be inflicted by some part of another person's body, a weapon, or the use of restraints. Although many think of IPV as being predominately physical in its manifestations, physical violence occurs less frequently than other forms of IPV and is usually preceded by other forms of control.[12]

Sexual violence is divided into three categories: (1) use of physical force to compel a person to engage in a sexual act against his or her will, whether or not the act is completed; (2) attempted or completed sex act involving a person who is unable to understand the nature of the act, to decline participation, or to communicate unwillingness to engage in the sexual act, for example, because of illness, disability, or the influence of alcohol or other drugs, or because of intimidation or pressure; and (3) abusive sexual contact, including unwanted touching or fondling.

Psychological/emotional violence involves trauma to the victim caused by acts, threats of acts, or coercive tactics. Psychological/emotional abuse can include, but is not limited to, such things as humiliating the victim, controlling what the victim can and cannot do, withholding information from the victim, deliberately doing or saying something to make the victim feel diminished or embarrassed, isolating the victim from friends and family, denying the victim access to money or other basic resources, and threats of physical or sexual violence.

Stalking generally refers to "harassing or threatening behavior that an individual engages in repeatedly, such as following a person, appearing at a person's home or place of business, making harassing phone calls, leaving written messages or objects, or vandalizing a person's property."[5] It is estimated that more than 1 million women and 371,000 men are stalked by intimate partners every year in the United States.[7]

As previously mentioned, both men and women can be victims of IPV, but this chapter will focus on female-directed IPV only.

IMPACT OF INTIMATE PARTNER VIOLENCE

The frequency of partner violence poses a serious public health challenge not only because of its prevalence but also because of the long-term impact of violence on women's short-term and longer term physical and psychological health. In general, the severity of abuse correlates with the impact on the woman's physical and mental health, multiple episodes and types of abuse over time are cumulative in their impact, and the effects of abuse persist long after the abuse has stopped.[13] It is important to note as well that the more severe the abuse, the stronger its relationship to negative health behaviors among victims, for example, high-risk sexual behavior, substance abuse, or unhealthy diet–related behaviors such as overeating or bulimia.[14,15]

IPV may result in acute physical injury but it also commonly leads to "functional" physical issues such as chronic pain syndromes, gastrointestinal problems, headaches or musculoskeletal pain.[13]

Gynecologic Outcomes

IPV has been associated with an increased risk of chronic pelvic or abdominal pain.[16–20] IPV, ongoing or in the past, has also been associated with increased risk for dyspareunia and this association is stronger when the abuse is/was sexual in nature.[16,17,21,22] Dysmenorrhea, menorrhagia, irregular bleeding, and endometriosis have all been found to be increased in victims of IPV in some studies as well.[18–24] Studies have also shown an increased risk for abnormal cervical cytology in victims of IPV, but this may be related, in part, to the increase in high-risk sexual behavior(s) that has been seen in some victims of IPV as a psychological response to the violence.[18,25,26] There does not appear to be an association between IPV and fibroids.[16] Some studies suggest an increased risk of sexual dysfunction and IPV.[19,27,28]

Adverse Pregnancy Outcomes

Domestic violence often begins or increases during pregnancy and the postpartum period.[29,30] It is estimated that 4 to 8% of women are abused at least once during pregnancy.[5] IPV during or in the immediate postpartum period incurs both maternal and perinatal risks.[31–33] Abused pregnant women have a three-fold higher risk of being victims of either attempted or completed homicide compared to their peers.[29] The risk for postpartum depression is two- to three-fold higher in women who have experienced psychological or physical abuse during pregnancy.[34] Pregnant women who experienced IPV at any time (prior to and/or during the pregnancy) are more likely to smoke or use other substances during the pregnancy.[35] Perinatal death is increased with IPV,[19,31,32,35–39] and there is a significant increase in the risk of low birth weight, NICU admissions, and low Apgar scores as well as preterm labor/delivery.[31,32,35,36,38–47]

Contraceptive Challenges/Unplanned Pregnancies

IPV has been shown to be significantly associated with unintended pregnancies.[48–53] Women with an unintended pregnancy have a higher risk (up to three times higher) of physical abuse compared to those whose pregnancy was planned.[29] Adolescent victims of physical or sexual dating violence are more likely to experience pregnancy than their peers.[54–57]

In some studies, women seeking abortions show elevated rates of IPV compared to the general population.[19,58–62] Women experiencing recent physical abuse were less likely to disclose an induced abortion to their partners, with a significant subset of abused women reporting fear of personal harm as the primary reason for nondisclosure.[59] A history of physical abuse by a male partner and a history of sexual abuse or sexual violence were found to be associated with repeat abortion among Canadian women.[63]

Despite the literature linking IPV and both unintended pregnancies and induced abortion, little quantitative data is available on differences in contraceptive use other than decreased use of condoms among abused versus nonabused women.[14,15] Young women attending a family planning clinic who were in a violent relationship were less likely to have used hormonal contraceptive at last intercourse.[64] Women in New Zealand who experienced IPV were more likely to report ever having used contraception than nonabused women but were also more likely to report that a partner had refused to use or tried to stop them from using contraception.[65] One study of adolescent dating violence did not find an association between contraception use at last intercourse and either current or past involvement in an abuse relationship.[56] However, consistent use of contraception is less likely among abused adolescents.[66]

Sexual Risk Behaviors and Sexually Transmitted Infections

High-risk sexual behaviors such as early age at first intercourse; trading sex for food, drugs, or money; substance use before last intercourse; increased number of sexual partners; and engaging in unprotected intercourse have been consistently associated with IPV.[53,67,68] Adolescent victims of physical or sexual dating violence were more likely to have first intercourse before the age of 15 years, to have three or more sex partners in the past 90 days, or to not have used a condom at last intercourse.[54,56]

Studies have consistently identified a significant association between IPV and either currently having a sexually transmitted infection (STI) or having a history of an

STI noted.[16,20,23,61] In one random sample of women in a large U.S. health plan, comparing women who reported IPV in the past year and women who reported never having experienced IPV, the women with reported IPV had a risk of having or having had an STI, including HIV/AIDS was three-fold higher compared to nonabused women.[69]

Interference With Health Care

Partner interference with health care is a relatively new area of research that may be of particular importance to physicians. In one study of 2027 women using two general questions on partner interference with health care, 17% of women abused in the past year reported that a partner interfered with their health care in contrast to 2% of nonabused women.[70] Women who had interfering partners were more likely to report poorer health (*OR* = 1.8, 95% CI = 1.0–3.2) even after controlling for recent violence and demographic characteristics.

Cancer and Cancer Screenings

Very little research has explored the effect of either current or past IPV on cancer prevention and control, although three studies investigating IPV and invasive cervical cancer found a statistically significant association.[23,26,71] Modesitt et al.[72] found that almost 50% of 101 women treated for breast, cervical, endometrial, or ovarian cancer reported a history of physical or sexual violence by a partner and 25% reported childhood abuse yet current abuse was rarely reported (2%). Women with cancer who had experienced IPV were less likely to have seen a physician in the year before diagnosis and were less likely to have had a Pap test or mammography. Further, lifetime IPV was strongly associated with being diagnosed at a more advanced stage of cancer.

Women experiencing childhood sexual abuse are significantly less likely to receive Pap testing at recommended intervals and have an increased risk for cervical dysplasia.[73,74] Pregnant teenagers with abnormal Pap results were more likely to report domestic violence and homelessness.[75] Recent severe physical abuse was associated with cervical squamous intraepithelial lesions and recent life stressors such as physical violence, sexual violence, and/or homelessness were associated with discontinuing free follow-up care for an abnormal Pap test.[76] Breitkopf et al.[77] found that having a mother or partner who encouraged follow-up care for an abnormal Pap was instrumental to women receiving follow-up care, whereas avoiding conflict with a partner was a reason for not receiving follow-up care. Those least likely to get follow-up care were those with family problems or conflicts with partners.

Mental Health

Physical or sexual IPV is often accompanied by emotional abuse as well.[78] The psychological consequences of IPV are many and include posttraumatic stress disorder (PTSD), anxiety, depression, interpersonal difficulties, substance abuse, eating disorders, low self-esteem and suicidal ideation or attempts even years after experiencing violence.[69,79,80] In one study of female victims of IPV, PTSD was found in 75% of the sample and major depressive disorder (MDD) in 54%; comorbid PTSD and MDD were common and led to greater maladaptive issues than either diagnosis alone.[81] If sexual violence is a component of the IPV, the likelihood that a patient will present with PTSD increases.[11]

Substance Use

Although studies have examined the issue of smoking and IPV in different populations and with different measures of IPV, adult women who experienced psychological, physical, or sexual abuse are consistently more likely to smoke than nonabused women.[82,83] The association between smoking and IPV is not consistent among adolescent victims of physical dating violence.[54]

Women who experienced recent or lifetime IPV are more likely to report problem drinking or drinking every day.[84,85] In a study of women attending internal medicine outpatient clinics in Mexico, current or prior alcohol or drug use by both the woman and her partner were associated with current IPV.[86] Women experiencing IPV were also more likely to report use of tranquilizers, sleeping pills, sedatives, antidepressants, and other recreational drugs.[87] Adolescent female victims of physical dating violence are more likely to report binge drinking.[54]

Quality of Life

Lifetime IPV is associated with at least one index of poorer quality of life (QOL) independent of the type of IPV experienced and appears to be consistently associated with poorer QOL in multiple domains.[52,55,88,89] Lifetime IPV (not necessarily current) remains a strong correlate of poorer current QOL and indicates the persistent effect of IPV in many cases long after women have left the abusive relationship. Understanding how IPV influences QOL and what factors mediate or moderate this relationship may be very important in efforts to improve mental and physical health.

Economic Impact of Intimate Partner Violence

IPV affects people of all ages, socioeconomic classes, ethnic groups, gender, and sexual preferences. Certain risk factors for IPV have been identified, but screening should be all inclusive and not simply focused on women with these risk factors. Women who experience IPV are more likely to live in economically vulnerable households and to live in disadvantaged neighborhoods, be unemployed, and miss more days from work.[90,91]

Women who experience IPV have more annual health care visits and higher annual health care costs.[92–94] These costs remain elevated even after the violence stops.

Estimates of the annual costs of IPV range from $2.3 to $7.0 billion for direct health care costs; the indirect costs of lost of productivity are approximately $1.8 billion.[91,95] Children of mothers with a history of IPV have more use of mental health services and primary care visits than do children of nonabused mothers.[96]

ROLE OF OBSTETRICIAN/GYNECOLOGIST IN ADDRESSING INTIMATE PARTNER VIOLENCE

Physician Training/Education in Intimate Partner

Robust education and training of physicians and other health care providers in IPV intervention and prevention improves screening awareness, familiarity with referral processes, and screening behaviors. The American Congress of Obstetricians and Gynecologists (ACOG) has provided robust practice guidelines related to screening for IPV for practicing OB/GYNs.[97] In their guidelines for women's health care, the following recommendation is made: "Clinician responsibilities in addressing IPV and domestic violence include the following: implement universal screening, acknowledge the trauma, assess immediate safety; help establish a safety plan, review options, offer educational materials, offer a list of community and local resources, provide referrals, document interactions, provide ongoing support at subsequent visits."[98]

With regards to screening during pregnancy, ACOG recommends that,[99] "psychosocial screening of all women seeking pregnancy evaluation or prenatal care should be performed regardless of social status, educational level, race, and ethnicity. Further, it is better to perform psychosocial screening at least once each trimester to increase the likelihood of identifying important issues and reducing poor birth outcomes."[99] There is evidence that women who are screened for psychosocial issues, including IPV, once each trimester are half as likely as women who are not screened to have a low-birth-weight or preterm baby.[100]

Although these guidelines can seem daunting, they may be implemented by various health care staff in the office, clinic, or hospital setting. It is important to train health care staff and providers with ongoing contact with the patient about the prevalence and the mental and physical consequences of IPV as well as the methods to screen for IPV. There are some data to suggest that patients are more likely to disclose information after they have been asked about violence repeatedly in the health care setting, thereby normalizing inquiry.[101] Studies also find that patients may be more likely to disclose personal IPV when questionnaires are self-administered, including computer-based screening.[102,103]

Screening Practices of Obstetrician/Gynecologists

Unfortunately, in the context of clinical practice, screening for IPV is not as thorough or universal as it should be. Various studies have looked at the screening(s) for IPV in both pregnant and nonpregnant patients, across various health care settings and by different specialties. Many of the published studies are questionnaire-based surveys and do not represent actual chart reviews and most of the data has been obtained from primary care physicians.

In studies by Chamberlain and colleagues[104,105] that evaluated screening practices of family physicians, internists, and obstetricians and gynecologists, they found that 86% of physicians screen "often or always" if a woman presented with an injury, whereas screening was only performed "often or always" at initial visits and annual exams in 6.2 and 7.5% of patients, respectively. Screening for IPV was found to occur in 17% of initial prenatal visits and 5% during return prenatal visits.[104]

In a national systematic sampling of 2400 obstetricians and gynecologists, emergency room physicians, internists, and family medicine physicians, Elliott and colleagues[106] found that only 6% of physicians screened all women, whereas ob/gyn physicians screened 20% of their patients. Similar results have been found in other studies as well.[107]

Clearly screening for IPV is not a frequent event in most physicians' offices. Although OB/GYNs appear to perform screening at rates greater than other specialties, the frequency and universal application of screening is still far from ideal. In one systematic review of barriers to IPV screening, five categories of barriers were identified: personal barriers, resource barriers, perceptions and attitudes, fears, and patient-related barriers.[108] The most frequent barriers were personal discomfort on the part of the provider, lack of provider knowledge about IPV, and time constraints. Many providers were not sure how to help the patient who is suffering from IPV and are concerned about privacy and safety issues for the patient, as well as personal safety concerns on the part of the provider.

Barriers for IPV screening for physicians have been addressed in several studies. Rodriguez et al.[109] categorized major barriers to physician identification of intimate partner abuse and referral of patients into three categories: patient-related barriers, mutual barriers, and provider-related barriers. About 82% of physicians believe that the patient's fear of retaliation was a barrier, 78% "lack of disclosure," 55% "fear of police involvement," and 52% "lack of follow-up." When components of "mutual barriers" were evaluated, "cultural difference," "lack of privacy," and "language differences" were felt to be barriers by 56%, 48%, and 39% of physicians, respectively. In the assessment of provider-related barriers, these authors noted that 39% of physicians cited "lack of training," 37% "lack of time," 30% "lack of resources/referrals," and 18% "a sense of inefficacy." Physicians who had received training in the past 3 years in intimate partner abuse were less likely to report the lack of information about local community agencies as a

major barrier (17% versus 33%) compared to those who had not received recent education. Perceived barriers were not consistently associated with physician specialty, sex, or reported screening practices.[109]

Addressing these barriers should improve screening. Higher screening rates are associated with a greater estimated prevalence of IPV in the physician's patient population, IPV training in the last 12 months or previously and confidence in one's ability to recognize victims.[106] Conversely, lower screening rates were associated with beliefs that the patient would volunteer the information as well as forgetting to ask the patients. Sitterding et al.[107] concluded that spouse/partner violence education in ANY stage of education was associated with a greater likelihood to screen all patients and that if IPV education had been provided during residency, the physician was three times more likely to screen for IPV. There is evidence that a strong practice commitment to IPV screening, specific policies for IPV screening in the office and ready access to professional support and management of IPV cases improves screening rates.[110]

In a study to assess "perceived preparedness" to provide preventive counseling, Park et al.[111] surveyed 928 final-year primary care residents (internal medicine, family practice, and obstetrics and gynecology) at 162 U.S. academic health centers. The residents were queried and overall felt better prepared to counsel about smoking (62%) and diet and exercise (53%) than about depression (37%), substance abuse (36%), or IPV (21%). In the study, ob/gyn residents were self-identified as being better prepared to counsel about IPV compared to graduating residents in internal medicine or family practice.

WHAT CAN PROVIDERS DO TO REDUCE THE IMPACT OF INTIMATE PARTNER VIOLENCE?

Addressing a Common Myth: Why Don't Women Leave?

Most women in violent or abusive relationship do leave. Divorce rates among women who have been abused are significantly higher than women in nonabusive marriages.[17]

The reasons some women give for staying in a violent or abusive relationship in the short term are situational and complex. Feelings of shame, guilt, love, low self-esteem, hopelessness, depression, coupled with economic dependency, lack of support systems, social isolation, and fear serve as significant impediments to "simply leaving." Negative experiences with medical professionals and the legal system are also reasons why some women stay in relationships that are dangerous. If other powerful persons cannot protect a woman, she may feel alone and unable to negotiate safety for herself and her children. Health care providers need to understand that the most dangerous time for women in abusive relationships is when women choose to leave that relationship; death by murder increases significantly within the month after women leave.[112] Providers should not encourage their patients to leave a relationship.[113] Pressuring women to leave the relationship is not the most effective therapeutic approach and may serve to recreate the dynamics of power and control present in the relationship in which IPV is occurring. Living in an abusive relationship and choosing to leave or make the abuser leave requires time, physical and emotional support, and legal and financial resources.

Providers need to foster trust and continuity of care while being mindful of appropriate boundaries. Patients have the right to make autonomous decisions and focusing the care that is provided on the patient's safety and health, rather than her choices in life, is ultimately more helpful. This approach is more in keeping with expectations women have of their providers when dealing with IPV (Table 18.1). The most important care a provider can provide following a disclosure of IPV (in the revelatory visit as well as follow-up ones) is an expression of empathy, acknowledgment, assessment of patient safety and working to ensure a continuing ability to provide support and assistance. An offer of referral to speak to someone about options and safety should be made at each visit.

Stages of Change: Leave-Taking Process

Just as with any decision to change, the process of reaching readiness to make the decision occurs along a continuum. The stages for change are often described as including a precontemplation period where the patient is not concerned about the situation, a time contemplation when change is considered but there is no readiness to do so, an arrival at a determination to make the change, and finally, the action step(s) of pursuing the change. People do not move linearly through these changes and may fluidly move back and forth between the various categories before ever truly instituting change.

TABLE 18.1 What Victims of Intimate Partner Violence Want From Providers

- An attitude that is nonjudgmental and compassionate
- Assurance(s) of confidentiality
- Recognition that IPV is a complex issue with no quick or easy resolution
- Discussions that are not rushed or glossed over
- Validation that the violence is undeserved
- Listening in a supportive manner
- Feedback that will help strengthen the patient's self-confidence
- Patience and understanding that progress through the issues must be done at the patient's own pace
- Shared decision making and respect for the patient's decisions (including the decision not to leave the relationship or press charges)

IPV, intimate partner violence.

Data from McCord-Duncan EC, Floyd M, Kemp EC, et al. Detecting potential intimate partner violence: which approach do women want? *Fam Med.* 2006;38:416–422; Chang JC, Cluss PA, Ranieri L, et al. Health care interventions for intimate partner violence: what women want. *Womens Health Issues.* 2005;15:21–30.

In a qualitative study with 20 women who had current or past histories of IPV, Chang[114] describes how women make changes to improve or seek safety and confirms the gradual process, which involves multiple steps and/or strategies. The types of action taken include education/information-seeking about community resources; interpersonal help-seeking such as disclosing abuse to family, friends, health care providers, clergy, or a counselor; self-empowering actions such as opening a bank account in her name only, storing an escape bag or a key with a friend or neighbor, or going back to school or work; and finally, seeking protection or separation by filing a legal restraining order, calling police, having a health care provider document abuse, or leaving.

In focus group interviews with women who had experienced IPV, the survivors advised providers to give a reason for asking their patients about IPV to reduce stigma and patient's suspicion.[115] One example of a reason might be "because violence or abuse can be a problem for many women and because violence or abuse can affect women's health, we ask all our patients about abuse." It is helpful to IPV survivors for providers to create an atmosphere of safety and support for disclosure. Disclosing IPV is very hard. Providers should only ask about IPV in a private room when the partner is absent, should make such inquiries when the patient is fully clothed, and take the time to ask the questions slowly and with concern. The physical environment is also important. Placing posters and other materials on IPV or sexual violence in both public and private view in the office and providing resources that address IPV, regardless of whether women disclose IPV or not, opens doors for women to talk about their experiences and their needs. Having resource cards available in the restrooms or providing cards with resource information or numbers to all patients with a statement such as "Many women experience partner violence. In this office, we provide this information card to all our patients. This card may be helpful to you, a friend, or a family member."[116]

Intimate Partner Violence Screening

ACOG and many other national organizations recommends universal or routine screening at annual exams, family planning visits, and preconception visits.[99,116,117] The literature clearly shows that women do not mind being asked about abuse.[118,119] In fact, not asking about IPV may adversely affect the physician–patient relationship.[120] More recently, research has shifted toward identifying the most productive mode with which to identify IPV and intervene appropriately. With the advent of computer-assisted interviewing technology as well as electronic medical records, new options for IPV screening are now available. In a recent review of computer-assisted screening for IPV, Renker[121] observed that in general, computer screening identified higher IPV rates than were observed for either written or interview screening. The prevalence of physical IPV when using computer-assisted methods ranged from 16 to 19% relative to <1 to 11% with written or interview formats. Clearly, computer screening will not work in all health care settings and for all women, yet this option ensures that women are "asked" the questions and some women benefit from the perceived anonymity of the computer versus disclosing IPV directly to a health care provider. The challenge of computer IPV screening is that of providing resources tailored to the individual patient's needs. A combination approach of computer screening with prompts to engage health care providers or other clinic staff to discuss the screening results and options might be a productive approach to ensuring screening and appropriate referrals.

How Should a Practice Implement a Screening System for Intimate Partner Violence?

Ideally, a screening system would be implemented in a collaborative fashion with nurses and other office personnel and would include linkages for referrals. A range of different screening modalities may be used such as patient self-directed responses via a computer system, a paper checklist, or having the health care providers directly ask the screening questions in a private setting.

Screening involves not only asking the right questions but also documenting findings *with patient consent* and providing information to victims about safety, options, and interventions. If a state has mandatory violence reporting laws, patients need to be informed that IPV disclosure will result in their case being reported. Clinicians may reach out to hospital or community-based organizations if they are not clear what state reporting mandates exist. Commonly, mandatory reporting is required if the IPV involves abuse of a disabled person, use of a weapon, abuse of an elderly individual, and abuse involving children. State policies vary on whether a situation in which a child witnesses a parent being abused is considered child abuse. However, verbal or physical violence that a child hears or sees is considered to be "witnessed violence." In some states, this term may be expanded to include not just the observation of the actual violence but also the effects of the violence.[122,123] Children who witness IPV may develop symptoms of PTSD.[124] Identifying IPV is an important means of preventing child abuse because IPV is a leading forerunner to child abuse.[125] If they are asked, many women will disclose IPV victimization in a pediatric setting.[126,127] Regardless of a state's reporting requirements, if child exposure to IPV is possible in a given situation, the clinician must try to ascertain how safe the home situation is and if the child may return to that home.

Reports of IPV need to be specific and detailed and, where permitted, should include quotes from the patient about the occurrence(s), nature of IPV, time of abuse, and the identity of the perpetrator. Patients

TABLE 18.2 The Clinician's Role in Cases of Intimate Partner Violence

- Make the diagnosis.
- Provide medical care and emotional support.
- Counsel the patient about the nature and course of domestic violence.
- Assess the safety of the patient and any dependents at home.
- Determine if the violence is escalating.
- Inform the patient about available support services.
- Document findings if the patient consents to this.
- Refer the patient to appropriate resource and counseling services.
- Assure the patient has follow-up.

Adapted from Chambliss LR. Intimate partner violence and its implications for pregnancy. *Clin Obstet Gyn.* 2008;51:385–397.

have the right to ask that information about IPV not be included in the chart, particularly if there is a possibility or fear of a possibility that this information may increase the risk of danger to the woman if the perpetrator becomes aware of it. Findings on physical exam should be objectively documented and described and if it is possible, photographs should be taken of injuries once the patient's written consent has been obtained to do so. If applicable, a rape kit should be obtained and documented.

What Questions/Screening Tools Are Available and Effective?

A variety of questionnaires for IPV screening exist and discussions and analyses of commonly used screening instruments exist.[128,129] Frequently used screening tools include the Abuse Assessment Screen (AAS), the "Hurt, Insulted, Threatened, or Screamed at" or HITS screener, the Partner Violence Screen (PVS), and the Woman Abuse Screening Tool (WAST). The Centers for Disease Control and Prevention has compiled a publication that includes a table of screening tool as well as the instruments themselves.[128] No single screening tool, however, has well-established psychometric properties and even the most common screening tools mentioned earlier have been evaluated in only a small number of studies.[129] Familiarity with the strengths and weaknesses of the four commonly used instruments will help a clinician determine which screening tool(s) should be used in their office setting.

TABLE 18.3 Perpetrator Characteristics That Are Associated With Increased Danger to the Patient

- Violent outside the home
- Violent to children
- Threatening to kill victim, children, self
- Escalating threats
- Using drugs—especially phencyclidine (PCP), crack cocaine, amphetamines, or alcohol
- Abusive during pregnancy
- Obsessive controlling relationship
- Has provoked serious prior injury
- Owns weapons, especially handguns
- Threatened others, including friends and/or family

From Campbell JC, Webster DW, Glass N. The danger assessment: validation of a lethality risk assessment instrument for intimate partner femicide. *J Interpers Violence.* 2009;24:653–674.

TABLE 18.4 Characteristics of the Victim Associated With Increased Danger to Herself

- Attempting to leave the relationship
- Has sought outside intervention
- Acknowledgment that she is afraid for her life
- Suicidal (with a plan, or with prior suicide attempts, or has means)
- Homicidal

From Campbell JC, Webster DW, Glass N. The danger assessment: validation of a lethality risk assessment instrument for intimate partner femicide. *J Interpers Violence.* 2009;24:653–674.

What to Do if My Patient Discloses Intimate Partner Violence?

The clinician's role in cases of IPV is summarized in Table 18.2. In assessing the safety level of the situation for the patient and any dependents, it is helpful to be aware of markers for increased danger to the patient from the perpetrator as listed in Table 18.3, as well as victim-related indicators that are associated with increased danger for herself and/or the perpetrator (Table 18.4). A Danger Assessment Tool has been developed and validated to predict the likelihood of lethality or near-lethality in IPV relationships.[130] Providers are often encouraged to help the patient develop a safety plan (Table 18.5) and provide her with the contact information for resource centers such as the National Domestic Violence Toll Free Hotline (1-800-799-7233) and the National Coalition Against Domestic Violence (http://www.ncadv.org) (see Table 18.6 for a list of additional resources). Many abusers carefully monitor women so reinforce the need to call or use the Internet at a safe time and place. In many communities, culturally specific community-based groups are

TABLE 18.5 Safety Plan for Intimate Partner Violence Victims

- Having an emergency kit with important documents,[a] keys,[b] money, and other essential items[c] that is stored outside the home in case there is a need to flee
- Determining in advance a safe place to go to regardless of the time
- Creating a well-known signal to alert children or neighbors to call 911
- Planning and knowing the escape route in situations where violence is escalating
- Review the safety plan frequently

[a]Marriage and driver's license, birth certificates, money, checkbooks, credit cards, ATM cards, car title, social security card, papers for documentation, passport, divorce papers, insurance papers, medical records, lease or rental agreements or house deed, address books, computer hard drives or memory sticks.
[b]Keys to the house, car, office, any friend's homes.
[c]Medications, hearing aids, and essential personal items.

TABLE 18.6 Resources for Intimate Partner Violence

Web

- www.ncadv.org/resources/FactSheets.php
- http://www.womenshealth.gov/violence-against-women
- http://www.cdc.gov/ViolencePrevention/intimatepartnerviolence/index.html
- www.futureswithoutviolence.org/

Telephone Resources

- National Domestic Violence Hotline: 1-800-799-SAFE (1-800-799-7233)
- The National Sexual Assault Hotline: 1-800-656-4673
- The National Teen Dating Abuse Hotline: 1-866-331-9474

National Domestic Violence Hotline number, 1-800-799-SAFE (1-800-799-7233), can provide clinicians in every state with information on local resources.

trying to assist their members that may be involved in IPV. Examples include Alianza for Latina women or SEARAC for IPV victims of Asian descent.

Patients may consider obtaining a protective order, which will legally prevent the perpetrator from contacting the woman. Usually, a legal advisor or advocate will help the woman navigate through this process. The effectiveness of such orders is mixed; some demonstrate an increase in abuse, whereas others show a decline.[131,132] Two meta-analyses of court-ordered interventions showed minimal success with a decrease in recidivism of only 5 to 7%, and there is evidence that attrition rates from intervention programs are high, with many of the perpetrators likely to be involved in IPV again.[133–135]

CLINICAL NOTES

- IPV is a pattern of coercive behaviors that may be found among heterosexual or same-sex couples and does not require sexual intimacy to be present, either currently or in the past, to occur.
- IPV is estimated to result in 2 million injuries to women and nearly 600,000 injuries to men on an annual basis.
- Most IPV physical assaults are relatively minor but it may result in death; IPV resulted in an estimated 2340 deaths in 2007, with 70% occurring in women and 30% in men.
- "Battering" involves severe and escalating violence with concurrent terrorization and increasingly controlling behavior by the abuser.
- "Common couple violence" is a more moderate form of IPV in which violence occurs occasionally and is usually triggered by frustration and/or anger.
- It is estimated that more than 1 million women and 371,000 men are stalked by intimate partners every year in the United States.
- IPV may result in acute physical injury but it also commonly leads to "functional" physical issues such as chronic pain syndromes, gastrointestinal problems, headaches, or musculoskeletal pain.
- IPV has been associated with an increased risk of chronic pelvic or abdominal pain.
- It is estimated that 4 to 8% of women are abused at least once during pregnancy.
- Women with an unintended pregnancy have a higher risk (up to three times higher) of physical abuse compared to those whose pregnancy was planned.
- Adolescent victims of physical or sexual dating violence are more likely to experience pregnancy than their peers.
- High-risk sexual behaviors such as early age at first intercourse; trading sex for food, drugs, or money; substance use before last intercourse; increased number of sexual partners; and engaging in unprotected intercourse have been consistently associated with IPV.
- If sexual violence is a component of the IPV, the likelihood that a patient will present with PTSD increases.
- Adult women who experienced psychological, physical, or sexual abuse are consistently more likely to smoke than nonabused women.
- Women who experienced recent or lifetime IPV are more likely to report problem drinking or drinking every day.
- Women who experience IPV have more annual health care visits and higher annual health care costs. These costs remain elevated even after the violence stops.
- ACOG recommends that, "psychosocial screening of all women seeking pregnancy evaluation or prenatal care should be performed regardless of social status, educational level, race, and ethnicity." It is also recommended that women be screened at least once each trimester for IPV.
- Patients may be more likely to disclose personal IPV when questionnaires are self-administered, including computer-based screening.
- Most women in violent or abusive relationship do leave. Divorce rates among women who have been abused are significantly higher than women in nonabusive marriages.
- The most dangerous time for women in abusive relationships is when women choose to leave that relationship; death by murder increases significantly within the month after women leave.

(continues)

- Providers should only ask about IPV in a private room when the partner is absent, should make such inquiries when the patient is fully clothed, and take the time to ask the questions slowly and with concern.
- If a state in the United States has mandatory violence reporting laws, patients need to be informed that IPV disclosure will result in their case being reported. Know what the laws are regarding IPV reporting for your area.
- Commonly, mandatory reporting is required if the IPV involves abuse of a disabled person, use of a weapon, abuse of an elderly individual, and abuse involving children. Know what the laws are regarding IPV reporting for your area.
- Identifying IPV is an important means of preventing child abuse because IPV is a leading forerunner to child abuse.
- A Danger Assessment Tool has been developed and validated to predict the likelihood of lethality or near-lethality in IPV relationships.
- Providers should help the patient develop a safety plan and provide her with the contact information for resource centers such as the National Domestic Violence Toll Free Hotline (1-800-799-7233).

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CHAPTER 19

Lifestyle Modification

Catherine Takacs Witkop

At the heart of every clinical recommendation to a patient lies a fundamental obstacle. When an individual walks out of her provider's office, she either consciously or unconsciously realizes that she will need to change some aspect of her life in order to comply with the recommended treatment. Whether it is as simple as remembering to take a pill once per day or as complicated as losing weight, exercising, or needing to measure blood sugar every day, some modification to her daily schedule and status quo will be required. Although lifestyle modification can be difficult, the evidence is clear in many areas that it works. What providers need to understand, however, is that their input and support is often more critical here than in the standard therapeutic relationship. In this chapter, we review the evidence supporting lifestyle modification as a legitimate approach for prevention and therapy, explore the theoretical basis for behavioral modification, and identify key areas in women's health where lifestyle modification can and should be recommended.

WHY LIFESTYLE MODIFICATION?

One of the best-studied areas to support lifestyle modification in prevention of chronic disease is in patients at risk for diabetes. Three large randomized controlled clinical trials of primary prevention of type 2 diabetes in three different countries have all demonstrated that maintenance of 3 to 5 kg (7 to 10 lb) of weight loss through diet and physical activity reduced the incidence of type 2 diabetes in high-risk individuals by 40 to 60% over 3 to 4 years.[1-3] The largest and most recent study, the U.S. Diabetes Prevention Program, performed at 27 clinical centers throughout the United States, randomized over 3000 patients to control, use of metformin, or lifestyle intervention (achieve and maintain 7% or greater weight loss through a low-calorie, low-fat diet and at least 150 minutes of moderate physical activity per week).[3] Over 3 years, the lifestyle intervention group lost an average of 5.6 kg and the incidence of diabetes was reduced by 58%. The number needed to treat to prevent one case of diabetes was 7 in the lifestyle management group versus 14 in the metformin-treated group. Most importantly, this risk reduction was similar in all ethnic, age, and BMI (body mass index) groups.[3] The two earlier studies also demonstrated success in the reduction of risk of type 2 diabetes.

Familiarity with these three studies is critical for health care providers because they provide evidence that lifestyle modification does work. The challenge is translating what was done in large randomized controlled trials with significant patient support into the reality of clinical care. Difficulties include (a) providing convincing education to the health care providers on the benefits of implementation of lifestyle modification in their practice, (b) identifying the patients who would most benefit from lifestyle modification, and (c) creating systemwide solutions for the implementation. This chapter will address these three issues, specifically as they relate to providers of women's health care.

LIFESTYLE MODIFICATION AS GOOD MEDICINE

Many providers have not received formal training in lifestyle modification, and only with an understanding of behavior change can a provider adequately address many of the issues that affect women's health. Lifestyle modification must begin during the initial visit of a patient. The studies on prevention of diabetes described earlier are proof that lifestyle modification works. Now, let's get to the heart of the matter.

MODELS OF BEHAVIOR CHANGE

Social cognitive theory (SCT) has been employed as the theoretical basis for a multitude of behavioral interventions. Its premise is that three factors—environment, person, and behavior—interact and a change in one affects the other two.[4] Interventions to change health behaviors have used this theory as a guide. Providers of women's health care can apply SCT to behavioral change counseling. A provider is not typically able to alter the patient's physical or social environment but may be able to make recommendations on how the patient can modify her surroundings or with whom she interacts. For example, encouraging an individual to spend her lunch break with a colleague who takes a walk rather than sits in the smoking area to have a cigarette can have a positive impact on smoking cessation. Another factor that can impact behavior is person. The variables within an individual that might impact behavior modification include behavioral capability (knowledge and skills to

BOX 19.1

Stages of Change Model

1. Precontemplation
2. Contemplation
3. Determination
4. Action
5. Maintenance
6. Termination

BOX 19.2

Process of Change

1. Consciousness raising—increasing awareness via information, education, and personal feedback about the healthy behavior
2. Dramatic relief—feeling fear, anxiety, or worry because of the unhealthy behavior, or feeling inspiration and hope when they hear about how people are able to change to healthy behaviors
3. Self-reevaluation—realizing that the healthy behavior is an important part of who they are and want to be
4. Environmental reevaluation—realizing how their unhealthy behavior affects others and how they could have more positive effects by changing
5. Social liberation—realizing that society is more supportive of the healthy behavior
6. Self-liberation—believing in one's ability to change and making commitments and recommitments to act on that belief
7. Helping relationships—finding people who are supportive of their change
8. Counterconditioning—substituting healthy ways of acting and thinking for unhealthy ways
9. Reinforcement management—increasing the rewards that come from positive behavior and reducing those that come from negative behavior
10. Stimulus control—using reminders and cues that encourage healthy behavior as substitutes for those that encourage the unhealthy behavior

engage in the behavior), outcomes expectancies, observational learning, and perceived self-efficacy. Perceived self-efficacy is often highest when fewer barriers are in place to prevent the behavior change. Providing a patient with the understanding to successfully deal with these factors is key to SCT.

The transtheoretical model (TTM) was originally developed by James Prochaska and Caro DiClemente and is the foundation of many of the behavioral interventions used in clinical medicine.[5] The theory assumes that all people go through six stages of change in the process of altering a behavior. The six stages of change and a short description of each are listed in Box 19.1. In the first stage, the precontemplation stage, the patient does not have plans to change her behavior in the near future and often does not even believe that she is at risk for any adverse outcomes related to her behavior. In this stage, motivational interviewing (discussed later) may be particularly useful. Asking a patient's permission to discuss the given behavior is recommended when she is in this stage because she may become angry and less likely to consider change in the future.

The contemplation stage follows. In this stage, the patient may begin to understand the connections between her behavior and potential adverse outcomes on her health. The obstacles to consider in this stage are knowledge gaps on options to change behavior and any doubts in self-efficacy. If the patient remains interested in change, the determination stage comes next when the woman makes a commitment to change behavior and makes concrete, actionable plans. Recognizing obstacles that may arise is critical during this stage and reassuring patients that relapses occur frequently will minimize the impact a relapse or pitfall may have on success of the behavioral change. During the action stage, the patient actually will make the change in lifestyle, but this may be followed by relapse. A visit with a provider if relapse occurs can help the provider guide the patient through any changes that could be made to reduce the risk of future relapse. Finally, the maintenance stage marks the last stage of change but is by no means the easiest. This stage requires ongoing evaluation, encouragement, and empathy.

The TTM also has identified 10 processes of change shown in Box 19.2. Once a provider is familiar with the model, he or she can identify the patient's stage of change and then identify what intervention might be most effective.

MOTIVATIONAL INTERVIEWING

Motivational interviewing (MI) was first described by William Miller in 1983 and later expanded by Miller and Stephen Rollnick in 1995. The definition of MI at that time was described as "a directive, client-centered counseling style for eliciting behavior change by helping clients explore and resolve ambivalence."[6] The techniques have continued to undergo refinement, but the overall goal of MI is to use reflective listening and other tools allow the patient to move through stages of change as described in the TTM. The following are the key points that best describe the spirit of MI as described by Rollnick and Miller[7]:

1. Motivation to change is elicited from the client, and not imposed from without.
2. It is the client's task to articulate and resolve his or her ambivalence about the behavior.
3. Direct persuasion is not an effective method for resolving the ambivalence.
4. The counseling style is quiet and eliciting. Avoid arguments and confrontation.

5. The provider is directive in helping the client examine and resolve ambivalence; further skills training to effect the behavior change may also be required, but those are not the goals of MI.
6. Readiness to change is not a client trait but a fluctuating product of interpersonal interaction.
7. The therapeutic relationship is more like a partnership than expert/recipient roles.

The key skills can be summarized by the OARS acronym:

Open-ended questions
Affirm
Reflect
Summarize

More details on how to receive training in MI can be found at www.motivationalinterviewing.com.[8]

In a meta-analysis of 72 randomized controlled trials on effectiveness of "motivational interviewing" in a variety of behavior changes, MI had a significant and clinically relevant effect in changing behavior in approximately 75% of the studies.[9] In a recent Cochrane systematic review of 14 studies and over 10,000 patients, MI was found to be effective for smoking cessation when given by general practitioners or trained counselors, and longer sessions (greater than 20 minutes) tended to be more effective than shorter ones.[10] MI has also been used effectively in changing behaviors related to alcohol and drug use and HIV risk behaviors. Based on the evidence, organizations have recommended that providers understand and utilize MI with their patients in the appropriate clinical settings.[11] Training in MI is not common in standard medical training programs, but providers should become familiar with it in order to have another tool in their toolbox for behavioral modification among their patients.

MI should not be confused with the more general "brief intervention." Miller and Sanchez developed the acronym FRAMES to help instruct providers in the brief intervention.[12] This approach includes the following:

- Feedback (Compare the patient's behavior with nonrisk behavior patterns.)
- Responsibility (It is her responsibility to make the change.)
- Advice (Give direct advice to change the behavior.)
- Menu (Identify "risk situations" and offer options for coping.)
- Empathy (Use a style of interaction that is understanding.)
- Self-efficacy (Help the patient develop strategies, implement them, and commit to change.)

Several of the components are similar to MI, but "give direct advice" is clearly what makes this intervention different. Although both have been demonstrated to be effective in studies on health behavior change, it is helpful to understand the difference when reading the literature. For example, in smoking cessation, the brief intervention has proved effective, but MI is recommended for smokers who are in precontemplation.

Whether MI or brief intervention is used, providers should know that Current Procedural Terminology (CPT) codes and Evaluation and Management (E/M) service codes have been developed for patient counseling. The provision of such codes allows for practices to prioritize the commitment to counseling that is necessary for successful behavioral modification.

TOBACCO USE

An estimated 21% of American adults (44.5 million people) smoke and more than 440,000 Americans die from tobacco-related causes each year; in other words, one in five deaths is related to tobacco use.[13] The Centers for Disease Control and Prevention (CDC) estimates that 18.3% of American women used cigarettes in 2008.[14] A recent report from the Global Youth Tobacco Survey (GYTS) indicates that although boys aged 13 to 15 years are currently more likely to use tobacco than girls of the same age, that gap is closing, and in many countries, there is no significant gender difference.[15] Despite a common misperception, lung cancer is responsible for one out of four cancer deaths in females (27,000 more annual deaths than breast cancer).[16] Smoking reduces a woman's life expectancy by 7 years. Smoking also has significant and multiple implications in pregnancy. These data indicate that women's health providers have an important role in reduction of chronic disease burden among women and that role does not necessarily involve performing a pelvic exam.

The first step is to identify women who are ready to quit. Pregnancy is often a time of increased motivation. Many studies have demonstrated that 20 to 30% of women attempt to stop smoking while pregnant, and up to 40% who actually quit do so before their first obstetric visit.[17] Pregnancy also provides a good example of how contextual educational material can improve outcomes. Although office-based cessation counseling session of 5 to 15 minutes with a trained provider can result in smoking cessation rate of 5 to 10%, the rate was 20% when pregnancy-specific materials were provided.[18]

Clinical Practice Guideline

The most recent U.S. guideline for treating tobacco use and dependence outlines recommendations for clinicians.[19] The compelling evidence is based on thousands of cessation studies and has shown that clinicians can make a difference, even with a minimal intervention. Evidence has shown, however, that effectiveness of person-to-person contact for counseling increases with treatment intensity. A quick reference guide for clinicians can be found at http://www.ahrq.gov/legacy/clinic/tobacco/tobaqrg.htm.[20] The 5 As and 5 Rs have

been demonstrated to result in long-term cessation rates (over 5 months) of 15 to 20%, as compared to 5% for smokers who try to quit on their own.[21] The 5 As are the five major components of the brief intervention (Box 19.3). This model is straightforward and can be used as a screening and intervention tool by providers without additional training.

For those who are unwilling to quit, MI has been shown to increase future quit attempts. By identifying a tobacco user's feelings, beliefs, ideas, and values about tobacco use, the provider can use the patient's own "change talk" (any ambivalence about using tobacco) and "commitment language" (certain intentions, even if not complete commitment to abstinence) to increase the patient's resistance to change.

The 5 Rs should be addressed for those who are unwilling to quit (Box 19.4).

ALCOHOL AND DRUG USE

Alcohol and drug abuse are a significant problem among American women. According to a recent report, 24% of women aged 15 to 44 years are binge drinkers.[22] These rates are lower among women greater than 26 years of age but continue to be a problem throughout a woman's lifespan. Heavy drinking is defined as drinking five or more drinks on one occasion on five or more days in the last 30 days, and the rates of heavy drinking among American women ranges from 2.4 to 10%.[23] Furthermore, 9.8% of nonpregnant women and 5.1% of pregnant women aged 15 to 44 years reported illicit drug use in the past month.

As in the case of screening for tobacco use, screening for alcohol and drug use needs to be universal and can be accomplished by adding a few questions to an intake form or incorporating reminders into an electronic medical record. The U.S. Preventive Services Task Force (USPSTF) recommends the use of a self-report screening test for alcohol disorders in the primary care setting.[24] Screening questions include the Cut down, Annoyed, Guilty, and Eye-opener (CAGE), the Tolerance-Annoyed, Cut down, Eye-opener (T-ACE), TWEAK (same as T-ACE questionnaire), Alcohol Use Disorders Identification Test (AUDIT), or the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Questionnaire. These are presented in Appendix 19.A. An effective mechanism for making referrals needs to be in place, even if it is only in the form of a handout.

Even more than with other chronic disease, such as diabetes, hypertension, or obesity, trust in the provider is necessary for any substance-use behavioral change to occur. Women are more likely to hide their substance abuse or alcohol problems than men and are more likely to see only a gynecologist for their routine medical care, making the job of their provider more difficult. Unfortunately, a provider's uneasiness with substance use screening and treatment and the patient's concern about legal ramifications, social stigma, etc, often make the relationship more challenging. Patients with substance abuse problems need to be treated with dignity and respect. Given the number of programs available to assist women (pregnant or not) struggling with substance use and abuse, providers need to become comfortable with what is an obligation as part of being a provider of women's health care.[23] Pregnant women with substance abuse problems present their own set of

BOX 19.3

5 As

1. **Ask** about tobacco use. Effective treatments exist that can produce long-term or even permanent abstinence. All health care providers should address tobacco addiction at every clinic visit. Strategies to accomplish this include expanding vital signs to include tobacco use, using status stickers, or indicating tobacco use status via the electronic medical record.
2. **Advise** to quit. In a clear, strong, and personalized manner, every tobacco user should be urged to quit. Patients who smoke may receive daily messages from friends, society, and the media to quit, thereby priming them for the provider's advice. The provider should clearly state that it is possibly the most important thing that the patient can do to improve her health. Furthermore, personalizing the message can include things like pregnancy, asthma, children's health complications, or its economic implications.
3. **Assess** willingness to make a quit attempt. "Are you willing to give quitting a try?" If so, the provider should provide intensive treatment or refer the patient to someone who does. Furthermore, educational information should be provided, particularly if the patient is pregnant, an adolescent, etc. If the patient is not willing at this time, see discussion on the 5 Rs.
4. **Assist** in quit attempt. Strategies for implementation include the following:
   - Help the patient with a quit plan (set a quit date; tell family, friends, and coworkers about quitting; anticipate barriers; remove tobacco products/remove herself from environments).
   - Recommend use of approved medications (Table 19.1).
   - Provide practical counseling (problem solving/skills training).
   - Provide intratreatment social support (provision of social support as part of treatment).
   - Help secure social support outside of treatment (extra-treatment social support).
   - Provide supplementary materials, quitline numbers, etc.
5. **Arrange** follow-up within the first week and then the first month. Congratulate smokers who are abstinent, and encourage those who have relapsed to try again; consider more intensive treatment if necessary.

TABLE 19.1 Drugs Used for Smoking Cessation

Medication	Cautions/Warnings	Side Effects	Dosage	Use
Buproprion SR 150 mg (prescription only)	Not for use if: • Using monoamine oxidase inhibitors • Using buproprion in any other form • There is history of seizures • There is history of eating disorders • There is increased risk of suicidality in children, adolescents, and young adults	Insomnia Dry mouth	Days 1–3: 150 mg once daily Days 4–end: 150 mg twice a day	Start 1–2 weeks before quit date and use for 2–6 mo
Nicotine gum (2 or 4 mg) (OTC)	Do not eat or drink 15 min before or during use	Mouth soreness Stomach ache	• 1 pc every 1–2 h • 6–15 pc/day • If <24 cigs/day, use 2 mg • If >24 cigs/day or chewing tobacco, use 4 mg	Up to 12 wk or as needed
Nicotine inhaler (prescription only)	May irritate mouth/throat at first but this improves with use	Local irritation of mouth and throat	• 6–16 cartridges/day • Inhale 80 times/cartridge • May save partially used cartridge for next day	
Nicotine lozenge (2 or 4 mg) (OTC)	Do not eat or drink 15 min before or during use One lozenge at a time Limit 20 in 24 h	Hiccups Cough Heartburn	• If smoke/chew <30 min after waking, use 4 mg • If smoke/chew >30 min after waking, use 2 mg • Wk 1–6 use one every 1–2 h • Wk 7–9 use one every 2–4 h • Wk 10–12 use one every 4–8 h	3–6 mo
Nicotine nasal spray (prescription only)	May irritate nose (improves with time) May cause dependence Not for patients with asthma	Nasal irritation	One dose is one squirt per nostril • May use 1–2 doses/h • 8–40 doses/day • Do NOT inhale	3–6 mo, taper at end
Nicotine patch (OTC or prescription)	Do not use with severe eczema or psoriasis	Local skin reaction Insomnia	• One patch/day • If >10 cigs/day, use 21 mg for 4 wk; 14 mg for 2–4 wk; and 7 mg for 2–4 wk • If <10 cigs/day, use 14 mg for 4 wk then 7 mg for 4 wk	8–12 wk
Varenicline	Use with caution with: Significant renal impairment Serious psychiatric illness Patients on dialysis Increased risk for depressed mood, agitation, behavior changes, suicidal ideation, and suicide	Nausea Insomnia Abnormal or strange dreams	Days 1–3: 0.5 mg each morning Days 4–7: 0.5 mg twice a day Days 8–end: 1 mg twice a day	Start 1 wk before quit date Use for 3–6 mo

SR, sustained-release; OTC, over the counter.
From U.S. Department of Health and Human Services. Clinical guidelines: treating tobacco use and dependence: 2008 update. http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/treating_tobacco_use08.pdf. Accessed May 2008, September 2013.

BOX 19.4

5 Rs

1. **Relevance**—Similar to a personalized message to quit, motivational interviewing can be used to identify how smoking cessation can be relevant to the individual.
2. **Risks**—Risks to the patient should be clearly described in terms the patient understands.
3. **Rewards**—are critical to success
4. **Roadblocks**—need to be identified; patients need to be encouraged, not discouraged
5. **Repetition**—As long as the patient is unwilling to quit, these Rs should be repeated.

challenges. The American College of Obstetricians and Gynecologists (ACOG) has addressed some of the ethical issues related to substance abuse in pregnant women.[23]

As in tobacco cessation, numerous studies have been performed on screening for and treating alcohol and substance abuse. MI based on the TTM model of behavior change has been found to be extremely effective in treating women with alcohol abuse and substance abuse.[25] The Brief Negotiated Interview and Active Referral to Treatment (BNI-ART) Institute is a program that encompasses behavioral change theory in a practical series of steps to deal with a patient struggling with addiction. The intervention algorithm can be found at http://www.ed.bmc.org/sbirt/docs/aligo_adult.pdf.[26] It is critical for providers to understand some of the differences in substance abuse among women as compared to men. For example, psychosocial antecedents in women which tend to

be more common than in male substance abusers include depression, anxiety, bipolar affective disorder, phobias, psychosexual disorders, eating disorders, and posttraumatic stress disorders (PTSD).[27] Such coexisting disorders make success in behavior modification significantly more difficult. Female substance abusers have a higher rate of lifetime history of sexual or physical abuse or assault, physical illness, an accident, or disruption in family life.[22] Family issues often present barriers to successful behavior change. For example, as opposed to men seeking treatment for a substance abuse problem who are often encouraged by their spouses, women often are in dependent relationships and their partners may threaten violence or leave the relationship if the woman seeks care.[28] Because the environment and social norms are so critical to behavior change as outlined earlier in the section on behavioral theory, these factors are often overwhelming barriers for a woman to seek care. Because of these differences between women and men, female treatment programs may be more appropriate to deal with issues that seem to affect female substance abusers more frequently.

OBESITY

Overweight (BMI ≥25) or obesity (BMI ≥30) now affects a majority of Americans, with the age-adjusted prevalence of these combined disorders estimated at 68% of American men and women in 2007 to 2008.[29] Women are slightly more at risk than men; the 2007 to 2008 National Health and Nutrition Examination Survey (NHANES) demonstrated that 35.5% of women are obese, with a greater risk in non-Hispanic black Americans and Mexican Americans.[29] Because overweight and obesity are associated with multiple other chronic conditions, including diabetes, hypertension, dyslipidemia, among others, weight issues are considered first, followed by recommendations for behavior modification for the other individual disorders.

As in tobacco use, readiness to change is an important factor in the success of behavior change. Therefore, once a diagnosis of overweight or obesity is made, it is important to ask the patient about past weight loss attempts as well as desire to lose weight. A full history should include the patient's current understanding of weight loss, dietary habits, exercise history, in addition to medical history (comorbid conditions), medications, surgeries, and family history. The diagnosis of obesity is most commonly defined by BMI. BMI = weight (kg) / (height [m])^2 or BMI = (weight [lb] × 703) / (height [in])^2. Appendix 19.B provides a BMI chart using US pounds and inches. A BMI between 19 and 25 kg/m^2 is considered ideal. BMI is a clinically useful measure and is most commonly used by medical providers. However, it does tend to overdiagnose obesity in young athletic women (with higher bone density and muscle mass) and underdiagnose it in the elderly. Skin calipers to measure skinfold thickness or underwater weighing can measure body fat percentage, but these are less available in physician's offices. People with body fat percentages greater than 20% in men and 30% in women are considered obese.

A thorough history is critical for the provider to make recommendations about lifestyle change. MI is also useful in determining how the patient feels about her weight and any ambivalence the patient has about her weight. A successful weight loss program, whether or not it includes pharmacotherapy, needs to include behavioral modification to be successful. This should include goal setting, self-monitoring, modification of one's environment, cognitive restructuring, and attempts to avoid relapse.[30] Behavioral treatment in individual or small group sessions can help enforce the behavioral modification and can be recommended if available.[31] However, with even basic knowledge of behavioral change theory, the provider can also help support the individual through her weight loss.

Modification of lifestyle typically includes change in diet and increase in physical activity. The basic principle of weight loss based on diet is that energy intake must be less than energy expenditure. Overall, consumption of approximately 500 fewer kcal per day will allow loss of about 1 lb (0.45 kg) per week. Weight loss goals need to be realistic and the means by which a patient is planning on reaching those goals need to be within her ability. Loss of 5 to 10% of current body weight (or 2 BMI units) over 6 months is a reasonable goal. Even modest weight loss is sufficient to reduce blood pressure, improve glycemic control and lipid profile, and decrease morbidity and mortality.[32–34] Involvement of a dietitian has been shown to facilitate weight loss in the office setting, supporting the notion of the importance of knowledge and tools for any behavioral change.[35] Patients will often ask what kind of diet will be most effective at meeting their goals. Low-fat diets traditionally restrict dietary fat intake to less than 30% of total calories, and very low-fat diets restrict to less than 15% of total calories from fat. Weight loss does occur with low-fat diets, but very low-fat diets may be difficult to maintain. In most studies, low-carbohydrate diets have demonstrated more weight loss than low-fat diets, at least in the first 12 months.[31] One potential side effect may be an increase in low-density lipoprotein (LDL) cholesterol, which in the population of overweight or obese patients could be detrimental in the long run. Other commercial diets are also popular. Two recent randomized controlled trials comparing several different commercial diets found similar weight loss within the first 6 to 12 months in all diets.[36,37] These two studies seem to suggest that as long as the basic principle of energy expenditure exceeding energy intake is applied and the patients are supported, weight loss is likely to occur.

A large meta-analysis demonstrated that increases in physical activity combined with caloric restriction result in greater weight reduction and fat mass versus lean mass balance than either alone.[38] Physical activity in particular does rely heavily on environmental factors.

Many women, with one or more jobs, children, and other life stressors, will find it challenging to fit in physical activity. Furthermore, many Americans live in areas where it may not be safe to exercise outside and may not have access to other exercise options. Again, MI may be beneficial in identifying the barriers to increased physical activity and some of the patient's own feelings about exercise. Without identifying and addressing both personal and environmental factors that are playing a role in a sedentary lifestyle, the provider will not be able to adequately promote behavior change.

Pharmaceutical and surgical management of obesity are outside the scope of this chapter, but lifestyle modification is also critical to the success of patients who are undergoing such treatment. A list of commonly used pharmaceutical agents for obesity can be found in Table 19.2.

Many of the lifestyle modifications discussed up to this point are relevant on their own merit, but most also impact cardiovascular disease (CVD) in women. CVD is the largest single cause of death among women (one-third of all deaths), and more women than men die every year from CVD in the United States.[39] In 2007, the American Heart Association (AHA) released an update on the most current clinical recommendations for the prevention of CVD in women 20 years of age and older. The guidelines for prevention of CVD in women include

TABLE 19.2 Drugs for Weight Loss Available as Adjuncts to Diets and Exercise for Treatment of Obesity

Generic Name	Usual Dosing (Adults)	US DEA Schedule	Adverse Effects and Precautions*
Pancreatic lipase inhibitor approved for long-term use			
Orlistat	120 mg three times daily with fat-containing meals A reduced dose of 60 mg is an option for patients who do not tolerate 120 mg	N/A	Cramps, flatulence, fecal incontinence, oily spotting, and absorption of fat-soluble vitamins may be reduced Rarely reported: severe liver injury, oxalate-kidney injury Contraindicated during pregnancy
Serotinin-2C receptor agonist approved for long-term use			
Lorcaserin	10 mg twice daily	N/A	Headache, URI, nasopharyngitis, dizziness, nausea Avoid in patients with severe hepatic or renal insufficiency (CrCl <30 mL/min) Contraindicated with ergot derivatives (e.g., ergotamine) Preferably avoid use with other serotonergic agents (including most antidepressants, triptan antimigraine medications, and some muscle relaxants) due to risk of serotonin syndrome* Contraindicated during pregnancy
Combination of phentermine-topiramate approved for long-term use			
Phentermine-topiramate	Initial: 3.75 mg phentermine/23 mg topiramate once daily in the morning for 14 days Then titrate based on response: 7.5 mg phentermine/46 mg topiramate daily for 12 wk, then 11.25 mg phentermine/69 mg topiramate daily for 14 days Maximum dose: 15 mg phentermine/92 mg topiramate daily; reevaluate after 12 wk	C-IV (due to phentermine component)	Dry mouth, constipation, paresthesias, depression, anxiety, elevated heart rate Abuse potential due to phentermine component Actions of topiramate component include inhibition of carbonic anhydrase; metabolic acidosis may result from renal bicarbonate loss. Maximum dose with moderate hepatic or renal impairment (CrCl <50 mL/min) 7.5 mg phentermine/46 mg topiramate once daily Upon discontinuation, tapering of dose over at least 1 wk is recommended Contraindicated during pregnancy, hyperthyroidism, glaucoma, patients taking MAO inhibitors
Noradrenergic sympathomimetic drugs approved for short-term use			
Diethylpropion	Immediate release: 25 mg three times daily before meals Controlled release: 75 mg every morning	C-IV	Increase in heart rate, blood pressure, insomnia, dry mouth, constipation, nervousness Abuse potential due to amphetamine-like effects May counteract effect of blood pressure medications Avoid in patients with heart disease, poorly controlled hypertension, pulmonary hypertension, or history of addiction or drug abuse Contraindicated in patients with a history of CVD, hyperthyroidism, glaucoma, MAO inhibitor therapy, agitated states, pregnancy, or breast-feeding
Phentermine	Immediate release: 15 to 37.5 mg daily or divided twice daily Orally disintegrating tablet (ODT): 15–30 mg once daily in the morning	C-IV	
Benzphetamine	Initial: 25 mg once daily; may titrate to 25–50 mg up to three times daily Maximum dose: 50 mg three times daily	C-III	
Phendimetrazine	Immediate release: 17.5–35 mg two or three times daily, 1 hr before meals Maximum dose: 70 mg three times daily Sustained release: 105 mg daily in the morning	C-III	

US DEA, United States Drug Enforcement Agency; CrCl, creatinine clearance; MAO, monamine oxidase; URI, upper respiratory infection; CVD, cardiovascular disease (arrhythmias, congestive heart failure, coronary artery disease, stroke, uncontrolled hypertension).
*For additional information on potential interactions of anti-obesity drugs with other medications, use Lexi-Interact program included with UpToDate.
From Bray GA. Drug therapy for obesity. In: Mulder JE, ed. *UpToDate*. Waltham, MA: 2013.

a list of seven lifestyle interventions recommended as clinical interventions.[39] Class I interventions included those that were "useful and effective" based on the literature. These include the following:

- Smoking cessation
- Physical activity (a minimum of 30 minutes of moderate intensity physical activity on most, and preferably all, days of the week; and a minimum of 60 to 90 minutes of the same for women who need to lose weight or sustain weight loss)
- Rehabilitation for women with recent cardiovascular event, angina, procedure
- Dietary intake (diet rich in fruits and vegetables; wholegrain, high-fiber foods; fish at least twice per week; saturated fat to less than 10% of energy; cholesterol to less than 300 mg/day; alcohol to no more than 1 drink per day; sodium intake to less than 2.3 g/day; consumption of trans fatty acids to less than 1% of energy)
- Weight maintenance/reduction (Maintain BMI between 18.5 and 24.9 kg/m^2 and waist circumference less than 35 inches.)

In clinical guidelines for both dyslipidemias and hypertension, lifestyle changes (as described earlier) are recommended initially unless the patient already has severe disease and sequelae. When comparing the impact on hypertension between different lifestyle changes, weight loss can result in about 5 to 10 points systolic/10-point diastolic reduction, reduction in sodium of 2 to 8 points, reduction in exercise of 4 to 9 points, and reduction in alcohol of 2 to 4 points. The USPSTF strongly recommends screening women aged 45 years and older for lipid disorders if they are at increased risk for coronary artery disease and provides a level B recommendation to screen women ages 20 to 45 years if they are at increased risk.[40] For dyslipidemias, the USPSTF states "although lifestyle modifications (diet and physical activity) are appropriate initial therapies for most patients, a minority achieves substantial reductions in lipid levels from changes in diet alone; drugs are frequently needed to achieve therapeutic goals. . . . Lipid-lowering treatments should be accompanied by interventions addressing all modifiable risk factors for heart disease, including smoking cessation, treatment of blood pressure, diabetes, and obesity, as well as promotion of a healthy diet and regular physical activity. Long-term adherence to therapies should be emphasized."[40] Reduction in dietary saturated fats and weight loss have been shown to reduce total cholesterol and low density lipoprotein C (LDL-C) by 10 to 20% in some patients, but total cholesterol reduction is usually in the 2 to 6% range.[40] Diabetes mellitus is another chronic medical condition for which diet and exercise are often prescribed. A recent meta-analysis sought to determine the effect of exercise on blood sugar control in type 2 diabetes.[41] Fourteen randomized controlled trials were evaluated and the review found that exercise improves blood sugar control, even without weight loss.

Obesity and Polycystic Ovary Syndrome

Certain conditions are of particular interest to women's health providers because they either occur uniquely in women or with greater morbidity in women. The first such disorder is polycystic ovary syndrome (PCOS), a condition in which over 50% of women are overweight or obese.[42] Although this has been discussed in Chapter 3, this chapter focuses on how the provider can assist the patient in lifestyle modification to positively impact a woman's health. Obesity in PCOS has been linked to more severe insulin resistance as compared to PCOS in lean women.[43] More severe insulin resistance furthermore is associated with increased androgen levels, suppressed sex hormone binding globulin (SHBG) (which then results in increased free testosterone), and increased rates of progression to impaired glucose tolerance (IGT) or diabetes.[44] Metabolic syndrome, which includes obesity, insulin resistance, hypertension, IGT or diabetes, hyperinsulinemia, and dyslipidemia, increases the risk of cardiovascular events two-fold and if diabetes is also present, increases it five-fold.[45,46] A recent concerning statistic is that the incidence of metabolic syndrome in adolescent women with PCOS was 37% in one recent nationwide study.[47]

Because PCOS encompasses a myriad of clinical symptoms and findings, even moderate amount of weight loss (at least 5% weight reduction) has the potential to positively influence many aspects of a woman's health. This fact is key in counseling obese patients with PCOS. Realistic goals should be set. In particular, waist circumference (with central adiposity being represented clinically by a waist–hip ratio of greater than 0.8) is a potential indicator of metabolic risk and may explain why even small amounts of weight loss overall may affect risk (if the weight loss is from the visceral fat).

What method of weight loss is best for patients with PCOS? The evidence for the effects of weight loss with diet alone demonstrates improvements in androgen levels, hirsutism, menstrual function and ovulation, as well as metabolic improvements in fasting insulin, glucose, and glucose tolerance.[48] When reported, total cholesterol and triglycerides were improved with weight reduction as well. Unfortunately, until now, very few studies have focused on exercise specifically for management of PCOS. In one small, recent study, patients either participated in a structured, supervised, individual, 30-minute treadmill session, three times per week, or were assigned to a group with dietary restriction alone.[49] Ovulation rates in the exercise group increased, and in those who did ovulate (in both groups), the study demonstrated improvements in weight, androgens, and insulin resistance. Exercise therefore may have a separate mechanism of action than diet in the modification of PCOS symptoms. Another study also supports lifestyle changes. In a randomized controlled trial of overweight women with PCOS, the group with weight loss through dietary restriction plus behavioral

TABLE 19.3 Guidelines for Dietary and Lifestyle Interventions in Polycystic Ovary Syndrome

1. Lifestyle modification is the first form of therapy, combining behavioral (reduction of psychosocial stressors), dietary, and exercise management.
2. Reduced-energy diets (500–1000 kcal/day reduction) are effective options for weight loss and can reduce body weight by 7 to 10% over a period of 6 to 12 months.
3. Dietary pattern should be nutritionally complete and appropriate for life stage and should aim for <30% of calories from fat, <10% of calories from saturated fat, with increased consumption of fiber, whole grain breads and cereals, and fruit and vegetables.
4. Alternative dietary options (increasing dietary protein, reducing glycemic index, reducing carbohydrate) may be successful for achieving and sustaining a reduced weight but more research is needed in PCOS.
5. The structure and support within a weight-management program is crucial and may be more important than the dietary composition. Individualization of the program, intensive follow-up and monitoring by a physician, and support from the physician, family, spouse, and peers will improve retention.
6. Structured exercise is an important component of a weight-loss regime; aim for >30 minutes/day.

Reprinted from an article in Reproductive BioMedicine Online by Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril.* 2009;92:1966–1982. (Table 6), with permission from Reproductive Healthcare Ltd.

modification had reductions in weight, improvements in menstrual function, increases in SHBG, and decreases in free testosterone compared with the control group.[50] Although numerous studies have investigated the potential benefits of modifying dietary macronutrient composition in weight loss, the evidence is inconclusive.[48]

Given the evidence, the Androgen Excess and Polycystic Ovary Syndrome Society recommends a number of lifestyle modification principles for obesity management in women with PCOS. These can be found in Table 19.3.[48]

Overall, research has consistently shown that even modest weight loss as a result of lifestyle modification can improve symptoms of PCOS. The data presented here can assist providers in demonstrating more concrete and short-term benefits of weight loss to women with PCOS, including improvements in hirsutism, ovulation, and fertility. Women who are resistant to behavior change may be encouraged by short-term successes. However, it is also important to stress that long-term maintenance of these successes may be difficult and many women may require more aggressive treatment in the form of pharmaceutical therapy or bariatric surgery. For these women, it is even more important that lifestyle modification is stressed and that ongoing support is provided by the medical community.

RISK BEHAVIOR SCREENING AND MODIFICATION FOR SEXUALLY TRANSMITTED INFECTIONS

Many visits to a woman's health provider present an opportunity to screen for and address risky sexual behavior. Unfortunately, many women do not recognize risky behavior until they have contracted a sexually transmitted infection (STI). Although STIs occur frequently in men as well, infections tend to cause greater morbidity in women. STI rates often depend on the demographics of a population, and it is worthwhile for providers to know the particular epidemiology for their population and the guidelines regarding screening and counseling for their population. For example, *Chlamydia* rates in 2009 among women between the ages of 20 and 24 years were 3273.9 per 100,000 women and the rate throughout the United States is nearly eight times for black women what it is for white women (1559.1 and 178.8 cases per 100,000 population, respectively).[51] Women's health providers should have a plan for screening and counseling in their population. Health professionals can access current information on the local epidemiology of STIs at http://www.cdc.gov/std/stats.[52]

Although it is important to address risky behavior at the time of diagnosis of an STI, every opportunity to provide education about STIs should be taken. The USPSTF recommends high-intensity counseling for all sexually active adolescents and for adults at risk for STIs.[53,54] The first step at any visit is an updated sexual history. Asking about specifics related to types of sexual activity engaged in is critical because many women do not understand that certain types of sexual activity (e.g., oral sex) may result in the transmission of STIs. A barrier to change in sexual risk taking is often that the patient does not believe she is at risk; for example, she may feel her peer group is at low risk or that she is not at risk because she has one partner who "doesn't have any diseases." Using MI in this setting can be extremely useful. Providing statistics about prevalence of certain STIs, especially if the epidemiology locally is known, can be helpful but only with certain patients. A frank discussion in which the provider is comfortable and nonjudgmental often paves the way for a healthy rapport with the patient and potentially more effective counseling. The counseling should be sensitive to the patient's age and culture, but providers should also be aware that stereotyping a patient's sexual behavior is also counterproductive. The Five Ps are a useful tool published by the CDC and are shown in Box 19.5.[55]

The USPSTF and most national organizations such as ACOG recommend screening sexually active women aged 15 to 26 years annually for chlamydia.[56] Cervical cytology screening guidelines should be followed as well.[57] A discussion of screening guidelines and a clear understanding of what tests are being ordered and why may help women understand consequences of STIs (e.g., infertility in the case of chlamydia and cervical cancer in the case of HPV). A patient should come away from her visit knowing what has been tested. Further information on obtaining a sexual history can be found at http://www.cdc.gov/std/treatment/SexualHistory.pdf.[58] Unfortunately, many women do not realize they are at risk for STIs until the day they are diagnosed with one. If a woman is diagnosed with an STI, she often has a

BOX 19.5

Ps—Problems Frequently Encountered by Former Smokers

1. **Lack of support for cessation**
   - Schedule follow-up visits or telephone calls with the patient.
   - Urge the patient to call the national quitline network (1-800-QUITNOW) or other local quitline.
   - Help the patient identify sources of support within his or her environment.
   - Refer the patient to an appropriate organization that offers counseling or support.
2. **Negative mood or depression**
   - If significant, provide counseling, prescribe appropriate medication, or refer the patient to a specialist.
3. **Strong or prolonged withdrawal symptoms**
   - If the patient reports prolonged craving or other withdrawal symptoms, consider extending the use of an approved medication or adding/combining medications to reduce strong withdrawal symptoms.
4. **Weight gain**
   - Recommend starting or increasing physical activity.
   - Reassure the patient that some weight gain after quitting is common and usually is self-limiting.
   - Emphasize the health benefits of quitting relative to the health risks of modest weight gain.
   - Emphasize the importance of a healthy diet and active lifestyle.
   - Suggest low-calorie substitutes such as sugarless chewing gum, vegetables, or mints.
   - Maintain the patient on medication known to delay weight gain (e.g., bupropion hydrochloride sustained-release [SR], nicotine replacement therapies [NRTs]—particularly 4-mg nicotine gum147—and lozenge).
   - Refer the patient to a nutritional counselor or program.
5. **Smoking lapses**
   - Suggest continued use of medications, which can reduce the likelihood that a lapse will lead to a full relapse.
   - Encourage another quit attempt or a recommitment to total abstinence.
   - Reassure that quitting may take multiple attempts, and use the lapse as a learning experience.
   - Provide or refer for intensive counseling.

(From Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update. Quick Reference Guide for Clinicians*. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; 2009. http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/reference/tobaqrg.pdf; Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; 2008. http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/treating_tobacco_use08.pdf

period of time when recommendations about behavioral change may be inappropriate. But her feeling of susceptibility may lead to behavior change.

Surveys assessing the link between a self-reported history of STI and subsequent sexual behavior have not demonstrated consistent effect of a self-reported STI on condom use.[59,60] Studies assessing outcomes related to behavior change are challenging at best. Adolescents are a particularly high-risk group for risky sexual behaviors. In the recent Youth Risk Behavior Surveillance System (YRBSS), among high school students throughout the United States, 34.2% reported being currently sexually active and 38.9% of those reported not using a condom during their last sexual intercourse.[61] Although providers may and should reach out to adolescents when the opportunity arises in the clinical setting, other means to encourage behavior modification in this setting may be appropriate. Adolescents are highly influenced by their peer groups and social marketing and use of multimedia to educate adolescents on the safe sex and consequences of risky sexual behavior should be considered in practices or communities with high rate of adolescents. Such creative means of providing a public health message may be more effective in this population than brief intervention during a clinical visit. Similar approaches may also be used in other areas such as tobacco cessation and substance use, which are more difficult for adolescents to speak openly about in a clinical visit.

CLINICAL NOTES

- Lifestyle modification efforts have been shown to work in large, randomized trials for the prevention of diabetes, a chronic disease state. It is an approach that can work in preventing and/or managing a variety of chronic health conditions.
- SCT is premised on the idea that interaction(s) between environment, persons, and a person's behavior occur in an ongoing manner and a change in one will affect the other two.

(continues)

- The stages of change model, or transtheoretical model, assumes there are six stages of change that occur before a behavior is permanently altered.
- Readiness to change is an important factor in the success of behavior change.
- The overall goal of motivational interviewing is to allow the patient to move through the six stages of change by helping them explore and resolve ambivalence about the change.
- Even more than with other chronic disease, such as diabetes, hypertension, or obesity, trust in the provider is necessary for any substance use behavioral change to occur.
- 20 to 30% of women attempt to stop smoking while pregnant, and up to 40% who actually quit do so before their first obstetric visit.
- Alcohol and drug abuse are a significant problem among American women; 24% of women aged 15 to 44 years are binge drinkers.
- Heavy drinking is defined as drinking five or more drinks on one occasion on 5 or more days in the last 30 days.
- Female substance abusers have a higher rate of lifetime history of sexual or physical abuse or assault, physical illness, an accident, or disruption in family life.
- For many women, family issues often present barriers to successful behavior change.
- A successful weight loss program, whether or not it includes pharmacotherapy, needs to include behavioral modification to be successful.
- Increases in physical activity combined with caloric restriction result in greater weight reduction and fat mass versus lean mass balance than either alone.
- Even modest weight loss as a result of lifestyle modification can improve symptoms of PCOS.
- The USPSTF recommends high-intensity counseling for all sexually active adolescents and for adults at risk for STIs.

Appendix 19.A
Alcohol Screening Questionnaires: AUDIT-C, CAGE, NIAAA, T-ACE, TWEAK

AUDIT-C

Question #1: How often did you have a drink containing alcohol in the past year?

• Never	(0 point)
• Monthly or less	(1 point)
• Two to four times a month	(2 points)
• Two to three times per week	(3 points)
• Four or more times a week	(4 points)

Question #2: How many drinks did you have on a typical day when you were drinking in the past year?

• 1 or 2	(0 point)
• 3 or 4	(1 point)
• 5 or 6	(2 points)
• 7 to 9	(3 points)
• 10 or more	(4 points)

Question #3: How often did you have six or more drinks on one occasion in the past year?

• Never	(0 point)
• Less than monthly	(1 point)
• Monthly	(2 points)
• Weekly	(3 points)
• Daily or almost daily	(4 points)

The AUDIT-C is scored on a scale of 0–12 (scores of 0 reflect no alcohol use). In men, a score of 4 or more is considered positive; in women, a score of 3 or more is considered positive.

CAGE Questions

1. Have you ever felt you should **Cut down** on your drinking?
2. Have people **Annoyed** you by criticizing your drinking?
3. Have you ever felt bad or **Guilty** about your drinking?
4. Have you ever taken a drink first thing in the morning (**Eye-opener**) to steady your nerves or get rid of a hangover?

Two affirmative responses are 77% sensitive and 79% specific for alcohol abuse and dependence but only 53 and 70%, respectively, for unhealthy alcohol use. From Maisto SA, Saitz R. Alcohol use disorders: screening and diagnosis. *Am J Addict.* 2003;12(suppl 1):S12.

T-ACE Questions

1. Tolerance
   - How many drinks does it take to make you feel high? (>2 drinks is an affirmative response.)
2. Annoyed, Cut down, Eye-opener

NIAAA (Questions Recommended for Youth Ages 14–18 Years)

1. "In the *past year, on how many days* have you had more than a few sips of beer, wine, or any drink containing alcohol?"
2. "If your friends drink, *how many drinks* do they usually drink on an occasion?"

Any days drinking and any friends drinking more than 3–4 drinks (2 for girls) in a day suggest the need for further discussion and advice.

TWEAK Test

1. How many drinks does it take to make you feel high?
2. Have close friends or relatives worried or complained about your drinking in the past year?
3. Do you sometimes take a drink in the morning when you first get up?
4. Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember?
5. Do you sometimes feel the need to cut down on your drinking?

The maximum score on the test is 7 points, with the first two questions counting for 2 points each and the last three 1 point each. Note about question 1: If a woman responds that it takes three or more drinks to feel high, she scores 2 points. If she responds "less than three," she scores 0 on the question. A total score of 2 or more on the test is an indication of harmful drinking and further evaluation is indicated.

Appendix 19.B
Body Mass Index Chart Determining Body Mass Index From Weight and Height

	Good Weights								Overweight				Obesity	
BMI (kg/m^2)	19	20	21	22	23	24	25	26	27	28	29	30	35	40
Height (inches)*	Weight (lb)*													
58″	91	96	100	105	110	115	119	124	129	134	138	143	167	191
59″	94	99	104	109	114	119	124	128	133	138	143	148	173	198
60″	97	102	107	112	118	123	128	133	138	143	148	153	179	204
61″	100	106	111	116	122	127	132	137	143	148	153	158	185	211
62″	104	109	115	120	126	131	136	142	147	153	158	164	191	218
63″	107	113	118	124	130	135	141	146	152	158	163	169	197	225
64″	110	116	122	128	134	140	145	151	157	163	168	174	204	232
65″	114	120	126	132	138	144	150	156	162	168	174	180	210	240
66″	118	124	130	136	142	148	155	161	167	173	179	186	216	247
67″	121	127	134	140	146	153	159	166	172	178	185	191	223	255
68″	125	131	138	144	151	158	164	171	177	184	190	197	230	262
69″	128	135	142	149	155	162	169	176	182	189	196	203	236	270
70″	132	139	146	153	160	167	174	181	188	195	202	209	243	278
71″	136	143	150	157	165	172	179	186	193	200	208	215	250	286
72″	140	147	154	162	169	177	184	191	199	206	213	221	258	294
73″	144	151	159	166	174	182	189	197	204	212	219	227	265	302
74″	148	155	163	171	179	186	194	202	210	218	225	233	272	311
75″	152	160	168	176	184	192	200	208	216	224	232	240	279	319
76″	156	164	172	180	189	197	205	213	221	230	238	246	287	328

The health risk from any level of BMI is increased if the patient has gained more than 5 kg (11 lb) since age 25 years or if the waist circumference is above 100 cm (40 inches) due to central fatness.
*Divide weight by 2.2 to convert pounds into kilograms; multiply height by 2.54 to convert inches into centimeters.

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CHAPTER 20

Complementary and Integrative Medicine

Juliet M. McKee

Complementary and alternative medicine (CAM) has come into common use with as many as 40% of adult Americans and up to 12% of children have used CAM in the last 12 months, and in the year prior to a 2007 survey, Americans spent $33.9 billion out of pocket, accounting for 11.2% of total out-of-pocket health care expenditures for the year.[1] The use of CAM side by side with conventional medicine is known as integrative medicine—the practice of medicine with the central focus on the physician–patient relationship and where healing, not curing, is the goal of therapy. Integrative medicine involves both conventional and complementary methods, first attempting natural and less invasive interventions before moving to more costly and invasive interventions while incorporating the patient's mind, body, spirit, and community in healing. Sometimes, the term "holistic medicine" is used to describe this type of practice.[2]

Offering advice to graduating medical students in 1889, Sir William Osler stated that putting the patient's interests first is the key to practicing medicine well. He stressed also the importance of physician self-care.[3] When the focus of a medical encounter is on the whole patient, not on the mode of practice or the doctor, a truly healing relationship becomes possible. In such a relationship, the patient is central and his or her doctor acts as a guide, advisor, or consultant.

Critics of conventional allopathic medicine argue that in its attempts to be more scientific, Western medicine "underestimates the individuality of patients and pigeonhole[s] (sic) them within a clinical pseudo-democracy."[4] This approach values typology, not variation and individuality. In trying to understand why the use of CAM is increasing, Xu and Chen[5] noted: ". . . biomedicine is at its limits nowadays when confronting degenerative diseases, stress-related diseases, and most chronic diseases, which are more related to the way we think and live than to bacteria and viruses. Most notably, biomedicine lacks reference to the self-healing capacity of the human mind and body and focuses on parts rather than the whole, treatment rather than prevention, the suffering disease rather than the diseased person."

Patients, like all human beings, want to be considered and treated as the individuals they are, and with the context of their lives, including their beliefs, histories, and experiences taken into account. Patients want a therapeutic approach to be based on both evidence as well as the idea that what differentiates each of us as individuals is central to our health and to healing. Healing is the work of the body, and the fundamental role of medicine is to help the body do this.

Providers should give their patients their undivided attention while they tell their story because there is an element of healing that comes with being truly heard. Authentic listening, the combination of active listening as well as reflecting back through a reconstruction of what the patient is thinking and feeling, provides a way for clinicians to help connect with patients, as well as their colleagues and even themselves at a myriad of levels.[6] Sometimes, in the simple act of telling of her story, a patient can begin to make connections and increase her understanding of her own situation. When the story is reflected back and clarifications or corrections are sought, the patient is reminded that they control the story, which often increases her insight(s) as well as the clinician's.

In 1948, the World Health Organization (WHO) defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity."[7] Physicians focus rightly on the biomedical well-being of patients, but this is not enough. Curing patients is a rarity and is not always possible. By focusing on the whole patient, listening to her story, understanding her social situation, and encouraging her to be an active partner in her health, providers can bring about healing.

The WHO definition notes that traditional medicine refers to the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, used in the maintenance of health and in the prevention, diagnosis, improvement, or treatment of physical and mental illnesses.[8] In 1992, the U.S. National Institutes of Health (NIH) Office of Alternative Medicine was established. The office was later upgraded to the National Center for Complementary and Alternative Medicine (NCCAM). In contrast to the WHO view of traditional medicine, NCCAM views CAM as "a group of diverse medical and health care interventions, practices, products, or disciplines that are not generally

considered part of conventional medicine" and freely admits the boundaries between CAM and conventional medicine are not absolute.[9]

The mission of NCCAM is "to define, through rigorous scientific investigation, the usefulness and safety of complementary and alternative medicine interventions and their roles in improving health and health care."[10] The three long-range goals of NCCAM are to advance the science and practice of symptom management; develop effective, practical, personalized strategies for promoting health and well-being; and help create and facilitate the creation of evidence used in decisions around CAM and its integration into health care and health promotion. There are five major objectives for NCCAM:

1. Advance research on mind and body interventions, practices, and disciplines.
2. Advance research on CAM natural products.
3. Increase understanding of "real world" patterns and outcomes of CAM use and its integration into health care and health promotion.
4. Improve the capacity of the field to carry out rigorous research.
5. Develop and disseminate objective, evidence-based information on CAM interventions.

Common categories of CAM include natural products (e.g., herbs, supplements, probiotics), mind and body medicine (e.g., tai chi), manipulative and body-based practices such as massage therapy, movement therapies such as Pilates, traditional healing or indigenous practices, energy therapy, and whole medical systems such as Ayurvedic or traditional Chinese medicine.

Western medicine, or allopathic medicine, is one system of health care. But there are other nonallopathic systems of health care and, like allopathic medicine, they also seek to improve health and well-being for patients, families, communities, and society. In many countries in Europe, naturopathic medicine is a mainstream approach and includes nutrition, exercise, hydrotherapy, and other forms of physical therapy. All medical systems are embedded in their cultures. As a result, certain aspects of a medical system believed to be meaningful to one group may be meaningless to another group in another cultural setting. When confronted with a new idea, a common reaction is to "translate" the idea into familiar terms or concepts. A key issue that is often overlooked is that "identical" or "translatable" terms often have different meanings in the context of different medical systems.

Medical pluralism is a term used to describe the existence of separate medical systems within a single society. The integrative medicine model seeks to integrate conventional, allopathic medicine with CAM modalities that have demonstrated strong scientific evidence of safety and effectiveness. In the efforts to create a more integrated model, however, critics note that under the guise of altruism and an interest in public safety, efforts are made to ensure that alternative practitioners are regulated, educated, and professionalized in a fashion similar to biomedical practitioners. This may constrain CAM's ability "to challenge, resist, and transform the hegemony and inequalities of biomedicine."[11]

This chapter provided a brief overview of several other systems of health care and various CAM modalities. In addition, there is a brief review of some of the CAM modalities used for common office gynecology concerns.

ASSESSING THE RISKS AND BENEFITS OF COMPLEMENTARY AND CONVENTIONAL THERAPIES

Navigating the worlds of conventional medicine and alternative therapies can be complicated. Many patients, including pregnant women, believe that natural remedies are safer and more effective than chemical drugs prescribed by doctors and they do not view the use of herbs or supplements as being chemical in nature.[11,12] Many patients do not disclose their use of CAM for fear of a negative response, the belief that clinicians do not need to know about it, or simply because they are not asked about it.[13] The problem is that some CAM treatments do have potential for risks and harm and may interact adversely with conventional pharmacologic therapies. These interactions may occur through a reduction in effectiveness of prescribed treatments or they may interact with the CYP cytochrome P450 enzymes in the liver that impact drug metabolism, particularly the CYP cytochrome P450 3A4 isoform (referred to as CYP3A4). Some herbs and supplements may accelerate or slow the action of these enzymes and thus impact the functional dose of a drug the patient is concurrently using.

One recent study showed that among 200 women receiving chemotherapy for ovarian cancer, 40% were using one or more CAM supplements that might interact poorly with their chemotherapy regimen and many patients took multiple supplements.[14] Only 42% discussed the use of CAM supplements with the conventional provider and even fewer 24% consulted with a CAM provider about the supplements they used. The study did not find that women were necessarily having ill effects from their use of CAM, but it does highlight that there is a high risk for ill effects and that further research in the use of ingestible CAM therapies with conventional medical therapies is needed.

One of the criticisms of CAM is that it lacks clinical trials and is not "evidence based"; however, this is not necessarily true. There are many peer-reviewed journals reporting on clinical trials, as well as many basic research endeavors into understanding and evaluating the mechanisms of action, safety, and efficacy of various CAM approaches. It is also critical to recall that because nonallopathic systems of health and medical care use

very different theoretical frameworks, it is extremely difficult, if not impossible in some instances, to use conventional research methodology where participants are selected by standard diagnostic criteria that are not easily applicable in alternative systems of care.

Patients will use and even ask about CAM therapies and they want their clinicians to be able to provide balanced, nonjudgmental recommendations. The Institute of Medicine recommends that health professional schools incorporate information about CAM into curricula at the undergraduate, graduate, and postgraduate levels.[15] Curriculum guidelines for integrative medicine have been published for medical students as well as residents, and some training programs have successfully created integrative medicine residency programs.[16,17] Currently, there are over 40 academic Integrative Medicine centers (go to Consortium of Academic Health Centers for Integrative Medicine at http://www.ahc.umn.edu/cahcim) conducting high-quality research and using the practice of integrative health care at their institutions.

It is not possible for a clinician to keep up with the burgeoning amount of evidence in conventional medicine and nonconventional medicine or nonallopathic health care systems. However, conventional practitioners do need to ask their patients about their use of CAM, be familiar with the various modalities, know what credible resources exist to refer patients to, and to develop relationships with accredited local and regional programs and practitioners that offer integrative or CAM approaches (Table 20.1).

INTEGRATIVE MEDICINE MODALITIES

Lifestyle

Lifestyle encompasses eating and exercise habits as well as how people cope with stress and relate to families and friends. Many patients would benefit from lifestyle modification that involves increasing physical activity and decreasing food intake. Helping patients achieve these lifestyle changes is difficult and has been addressed in the chapter on lifestyle modification (see Chapter 19). If all physicians would address lifestyle changes at EACH and every patient visit, meaningful change could eventually be achieved for many patients.

Food is a fundamental and essential element to the well-being of everyone. There is still a paucity of education around nutrition in medical training, and new research frequently changes recommendations, so keeping abreast of what to tell patients is difficult. Most people should be taking in five servings of vegetables and four servings of fruits daily. This may sound like a lot; however, when the appropriate serving size of either a fist or a deck of cards is taken into account, this may be easier to accomplish than on first glance.

Carbohydrate intake should be modified to include very few simple or refined carbohydrates and to maximize the amount of whole grains consumed. Fiber is essential, and taking in the recommended fruit and vegetable servings as well as plenty of whole grains has been shown to decrease the risk of diabetes, cardiovascular disease, and possibly colon and breast cancers.[18]

Women should be encouraged to consume plant sources of protein, such as soy. If they choose to consume animal sources of protein, fish and chicken should predominate and red meat should be consumed rarely.

High-quality fats are an important component of the diet. Poor-quality fats, such as trans fats, butter, and margarine should be eliminated from the diet entirely because they increase triglycerides and inflammatory mediators in the blood.[19] This can lead to a prothrombotic state with an increased risk for cardiovascular disease.[20] A greater propensity for increased endothelial inflammation arises after a high-fat meal in persons with abdominal obesity and hypertriglyceridemia.[21] Olive, canola, and grape-seed oils are healthy alternatives to poor-quality fats. Omega-3 fatty acids have been shown to decrease cardiac death and all-cause mortality in coronary heart disease patients.[21a] Recommendations call for women to eat at least three servings of fatty fish, such as salmon or cod, or consider the addition of supplements with purified fish or flaxseed oils.[22]

Many "diets" may be found in the literature, and patients are likely to ask for recommendations about them. In general, the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean diet provide an excellent starting place for dietary interventions for patients. The Mediterranean diet is an example of a healthy diet that encourages high consumption of fresh fruits and vegetables as well as whole grains and healthy fats such as olive oil. Several good clinical studies have shown that women who follow the Mediterranean diet when combined with a healthy lifestyle and exercise have decreased all-cause mortality.[23,24] Evidence has shown that this type of diet decreased

TABLE 20.1 Federal Resources on Complementary and Alternative Medicine for Providers and Patients

Federal Resources for Providers

National Center for Complementary and Alternative Medicine: nccam.nih.gov/health/providers
NCCAM Clinical Digest: nccam.nih.gov/health/providers/digest
Online Continuing Education Series: Video lectures available for CME/CEU credits: nccam.nih.gov/training/videolectures
OCCAM website: cam.cancer.gov

Resources for Patients

National Center for Complementary and Alternative Medicine: nccam.nih.gov; Toll-free clearinghouse: 1-888-644-6226
NCCAM Time to Talk Tips: nccam.nih.gov/health/tips
Medline Plus: medlineplus.gov
OCCAM website: cam.cancer.gov

incidence of cardiovascular disease,[25] certain cancers,[26] and obesity.[27] More information can be found at http://dashdiet.org/ and http://www.mayoclinic.com/health/mediterranean-diet/CL00011/.[25–27]

Moderate-to-intense physical activity for 30 to 60 minutes a day is recommended for almost all patients. This can include housekeeping activities such as vacuuming, washing floors, and walking dogs as moderate activities and mowing lawns and jogging as intense activities. Many people are quite sedentary, and some forget that modifying simple activities can greatly increase caloric output. Simple habits, such as parking farther away from store entrances or taking the stairs can increase physical activity in sedentary patients—anything to get them moving! When making recommendations for patients to increase exercise, the doctor often finds it helpful to learn what the patient enjoys doing and to invite her to help set exercise goals that are attainable.

Mind–Body Interventions

The mind has a powerful connection to the body, so addressing spiritual and mental health is an important part of integrative medicine. Mind–body therapies focus on the relationships among the brain, mind, body, and behavior, and their effect on health and disease. These approaches encompass a large group of techniques such as hypnosis, meditation, yoga, biofeedback, tai chi, visual imagery, acupuncture, massage therapy, and spinal manipulation, just to name a few. As research expands, there is a growing body of evidence that suggests a variety of interactions between the central nervous system (CNS), the endocrine, immunity, and peripheral autonomic nervous systems that may provide insight into the mechanisms of action by various mind–body approaches.

More than 3000 studies have shown a benefit from relaxation.[28] Thus, giving attention to behaviors that will reduce stress and create the relaxation response can positively impact well-being. These techniques can be taught and learned. Like most things, regular practice improves performance and has been shown to have long-lasting, positive effects on health.

Mind–body approaches are used in a variety of conditions associated with chronic pain, although evidence of their efficacy varies. Pain perception occurs in many centers in the brain, including the regions that are involved with attention, beliefs, conditioning, mood, emotion, stress, and cognition (see Fig. 20.1). Mind–body approaches to chronic pain work at one or more of the levels of the experience of pain and may have synergistic effects.[30] The feelings of stress, fear, and depression that often accompany chronic pain may amplify the perception of pain and the pain perceived may exist even in the absence of demonstrable tissue damage. A set of guiding principles relating to psychological factors and the management of pain has been created based on scientific evidence and is found in Table 20.2. A variety

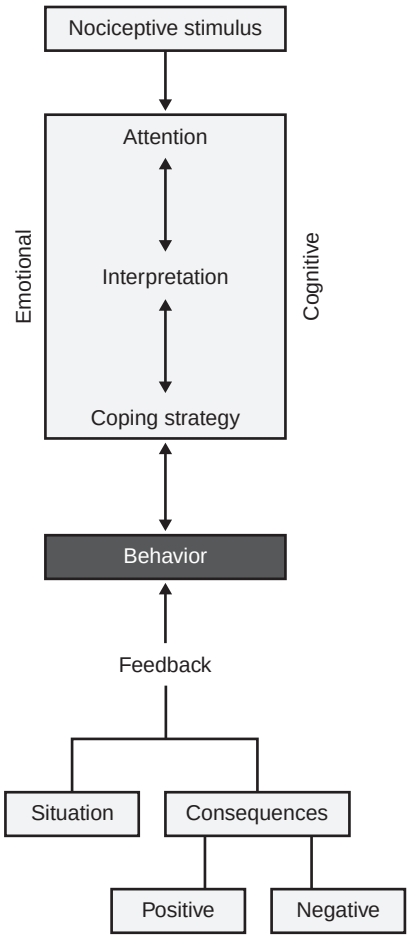

FIGURE 20.1 Pain perception pathways. (Reproduced with permission from Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. *Phys Ther*. 2011;91:700–711.)

of mind–body interventions have been advocated for use in the management of chronic pain. The relaxation response may be associated with greater pain tolerance and mindfulness-based approaches may lessen the impact of the hypervigilance and emotional reactivity linked to the genesis of chronic pain and allow for the development of acceptance (not resignation) of chronic pain symptoms, making it easier to focus on other experiences, participation in valued activities, and pursuing personally relevant goals.[31]

In one review of randomized trials using psychosocial interventions for chronic pain, group-delivered courses that had health care professional input showed more benefit.[32] Some mind–body skills are easily used in general practice, whereas others may require more extensive training.

In an interesting randomized study, participants who listened to a guided imagery CD preoperatively reported less pain and anxiety postoperatively and were discharged earlier from the postoperative anesthesia care unit (PACU).[33] Astin et al.[34] reported that presurgical mind–body programs reduced pain, anxiety, drug requirements, and days in the hospital. Such low-risk and

TABLE 20.2 Ten Guiding Principles Relating Psychological Factors to the Management of Pain

Treatment Phase	Number	Guiding Principle	Clinical Implications
Assessment	1	Psychological factors that may affect pain outcomes are not routinely assessed by many treating clinicians.	Better methods of screening and early intervention are needed to improve feasibility and utility in usual care settings.
	2	Persistent pain naturally leads to emotional and behavioral consequences for the majority of individuals.	Psychological concepts of learning can be useful to provide empathy and support without reinforcing pain behavior.
	3	Clients who are depressed or have a history of depression may have more difficulty dealing with pain.	A brief assessment of mood symptoms should be part of routine screening and intake procedures for pain conditions.
Treatment planning	4	Persistent pain problems can lead to hypervigilance and avoidance, but simple distraction techniques are not enough to counter these behaviors.	Clinicians should avoid inadvertent messages that escape or avoidance from pain is necessary in order to preserve function.
	5	Individuals hold very different attitudes and beliefs about the origins of pain, the seriousness of pain, and how to react to pain.	Assessment and treatment planning should take into account individual differences in pain beliefs and attitudes.
	6	Personal expectations about the course of pain recovery and treatment benefits are associated with pain outcomes.	Providing realistic expectations (positive, but frank and not overly reassuring) may be a very important aspect of treatment.
	7	Catastrophic thinking about pain is an important marker for the development of long-term pain problems as well as for poor treatment outcome.	Clinicians should listen for expression of catastrophic thoughts and offer less-exaggerated beliefs as an alternative. A brief assessment might be part of routine intake procedures.
Implementation	8	Personal acceptance and commitment to self-manage pain problems are associated with better pain outcomes.	Overattention to diagnostic details and biomedical explanations may reinforce futile searches for a cure and delay pain self-management.
	9	Psychosocial aspects of the workplace may represent barriers for returning to work while pain problems linger.	Return-to-work planning should include attention to aspects of organizational support, job stress, and workplace communication.
	10	With proper instruction and support, psychological interventions can improve pain management outcomes.	Psychological approaches can be incorporated into conventional treatment methods but require special training and support.

From Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. *Phys Ther.* 2011;91:700–711.

high-benefit interventions should become the standard of medical care. Other uses of mind–body therapies for various clinical conditions may be found in Table 20.3.

Dietary Supplements

Plants have been used for thousands of years for medicinal purposes and all cultures use botanicals for purposes of healing. Over time, standardized pharmaceutical drugs have replaced herbal therapies in the United States, Europe, and other areas of the world. In the first half of the 20th century, herbs were included in the U.S. National Formulary and U.S. Pharmacopoeia.[35] After 1962, herbal medicines were reassigned to the category of food supplements, which have a lower threshold of required evidence for demonstrating safety.

In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA), which defined dietary supplements as a product containing one or more of the following: a vitamin, mineral, amino acid, herb, other botanical concentrate, metabolite, constituent, or extract, and it placed supplements in a category distinct from drugs. Supplements are required to carry the following statement on their labels: "This product is not intended to diagnose, treat, cure, or prevent any disease"; however, this does not preclude their manufacturers from making health claims, for example, "promotes good eye health." Manufacturers of supplements are not required to prove efficacy, safety, or quality of their products prior to marketing or selling them. They are also not required to provide the FDA with any postmarketing data on adverse events. Although this requires the FDA to prove a product is unsafe or not effective and not many supplements have been removed from the market, some have; for example, ephedra, androstenedione, and PC-SPES. Adverse events may be reported to the FDA MedWatch program at 1-800-FDA-1088, online at www.fda.gov/safety/medwatch, by faxing 1-800-FDA-1078, or through the mail.

In 2007, the U.S. Food and Drug Administration (FDA) issued new rules that required good manufacturing practices (GMPs) for supplement makers to be phased in from 2008 to 2010. These rules required that supplements be properly labeled, free of adulterants, and made according to specified standards regarding equipment and personnel. There is still a great deal of flexibility for the manufacturers to choose the quality criteria they will follow, however. There is substantial variation in the quality of commercially available products in the United States as a result. Many things will determine the quality of a supplement, particularly one that is plant derived such as the plant species used, the parts of the plant that are used, harvesting and storage conditions, and processing. These variations may impact the supplements safety, efficacy, and clinical usefulness.

TABLE 20.3 Overview of Mind-Body Therapies for Various Clinical Conditions

Condition	Mind-Body Therapy	Level of Evidence[1]	Comment
Surgery/Procedure: Pain	Hypnosis	A	Guided imagery may reduce length of hospital stay
	Guided imagery	B	
Surgery/Procedure: Anxiety	Hypnosis	B	
	Guided imagery	B	
Cancer: Pain	Hypnosis	A	Guided imagery "B" when combined with other therapies
	Guided imagery	B	
Cancer: nausea and vomiting (chemotherapy)	Guided imagery	A	Guided imagery "A" when combined with other therapies
	Hypnosis	B	
Cancer: Psychological symptoms (e.g., mood, anxiety, stress)	Guided imagery	A	
	Mindfulness meditation	A	
Chronic pain (various etiologies)	Guided imagery	B	
	Mindfulness meditation	B	
	Hypnosis	B	
Fibromyalgia	Mindfulness meditation	B	
	Guided imagery	C	
Migraine headache	Biofeedback	A	EMG biofeedback or thermal biofeedback plus relaxation
	Guided imagery	C	
Tension headache	Biofeedback	B	
	Guided imagery	C	
Irritable bowel syndrome	Hypnosis	A	
	Guided imagery	C	
Hypertension	Biofeedback	B	Thermal or electrodermal biofeedback best, add relaxation or cognitive therapy to biofeedback
Raynaud's phenomenon (primary)	Biofeedback	B	
Anxiety disorders	Mindfulness meditation	B	
Depression	Mindfulness meditation	A	MBCT or MBSR
Insomnia	Mindfulness meditation	B	Progressive muscle relaxation and combination of mind-body therapies also shown effective
	Biofeedback	C	
	Hypnosis	C	
Urinary incontinence	Biofeedback	A	Stress, urge, mixed or post-prostatectomy
Fecal incontinence	Biofeedback	B	First-line therapy
Chronic constipation (pelvic floor dyssynergia)	Biofeedback	A	First-line therapy
Asthma	Biofeedback	C	
	Hypnosis	C	

[1]Level of evidence: A, high quality: consistent evidence from randomized trials or overwhelming evidence from other sources; B, moderate quality: evidence from randomized trials with important limitations or very strong evidence of some other form; C, low quality: evidence from observational studies or randomized trials with serious methodologic flaws.

EMG, electromyographic; MBCT, mindfulness-based cognitive therapy; MBSR, mindfulness-based stress reduction.

Elkins G et al. Mind-body therapies in integrative oncology. Curr Treat Options Oncol. 2010 Dec;11(3–4):128–40. [PMID: 21116746]

Nguyen LT et al. Use of mind-body medicine and improved self-rated health: results from a national survey. Int J Person Centered Med North America. 2011 Sept; 1. http://ijpcm.org/index.php/IJPCM/article/view/111.

Wahbeh H et al. Mind-body interventions: applications in neurology. Neurology. 2008 Jun 10;70(24):2321–8. [PMID: 18541886]

In Europe, herbal medicine is often referred to as phytotherapy and it is commonly integrated with conventional medicines. German physicians receive training in medical school in herbal medicine and this is included in their testing for licensure. Regulation of herbal products in Europe is greater than in the United States and a 2004 EU directive requires manufacturers of nonprescription herbal products to register and license all products with the European Agency for the Evaluation of Medicinal Products. Premarket evaluations of efficacy and safety are required and postmarketing surveillance by the companies is required, as is the reporting of serious adverse events.

There have been reports of herbal medicines containing pharmaceutical agents; for example, PC-SPES was used for prostate cancer by some and was found to contain diethylstilbestrol (DES), warfarin, and indomethacin.[36] Reports of contamination with lead, mercury, arsenic, and other heavy metals in imported herbal products have also been reported.[37,38]

Most Americans use dietary supplements, with usage rates ranging from 40 to 70% in the general population.[39,40] In most reports, women use more dietary supplements than men; in at least one study, usage among elderly women was reported to be as high as 84%.[41]

According to one nationally representative survey, the most commonly used supplement is fish oil or other omega-3 supplements.[42] In that same survey, the most common reason people used supplements were to "feel better" (41%), "improve overall energy levels" (41%), and to "boost your immune system" (36%). When asked if public health authorities declared the use of the supplement they were taking to be ineffective, only 25% of respondents said they would stop using it, a finding similar to an earlier 2001 study.[43]

Women often seek advice about supplements from their friends, family, and the Internet.[44] The Office of Dietary Supplements (ODS) at the NIH (www.ods.od.nig.gov) offers information on individual vitamins, minerals, and other dietary supplements and a link to a new PubMed subset, "Dietary Supplements," available online at http://ods.od.nih.gov/Research/PubMed_Dietary_Supplement_Subset.aspx.

Clerks at health food stores routinely advise patients about dietary supplements. In one study, a researcher posed as the daughter of a woman recently diagnosed with breast cancer and asked for advice from 40 separate health food stores in the area. In all instances, she was given advice about what supplements to take.[45] In a more recent study, researchers reporting classic symptoms of type 1 diabetes asked for advice from health food store employees: 75% of the clerks recommended a natural supplement, only 25% of them recommended urgent physician evaluation, and 25% of them advised NOT to seek medical attention.[46] Researchers found that fewer than half health food store clerks surveyed inquired about the use of other drugs and supplements before recommending St. John's wort for depression, which is known to have some serious drug interactions.[47]

The use of dietary supplements to lose weight is extremely popular, but the efficacy for most of these supplements is not proven. Chromium is a supplement that has gained increasing attention for use in weight loss programs; it is an essential trace element, and in human tissues, is necessary for the metabolism of fats and carbohydrates. Reports suggest that chromium increases insulin sensitivity, may potentiate the actions of insulin at the receptor, decrease food cravings, and increase metabolic rate.[48–51] A recent review and meta-analysis showed that although there is a *statistically* significant difference in body weight and percentage of body fat between chromium use and placebo, the *clinical* relevance of this is unclear (weight loss was less than 5% of body weight), future clinical trials should last at least 16 weeks, and there are concerns with adverse events such as renal impairment, hepatotoxicity, vertigo, weakness, nausea, and vomiting.[52–54]

In light of the evidence that diets rich in fruits and vegetables, which are replete with various vitamins and antioxidants, are associated with a reduction in risk for cardiovascular disease (CVD), there is also strong interest in the use of vitamins and antioxidants as supplements to prevent CVD.[55] Some estimates note that if fruit and vegetable intake were increased to 600 g per day, the worldwide burden of disease due to ischemic heart disease could be reduced by 31% and by 19% for ischemic stroke.[56] Meta-analysis from randomized controlled trials looking at the efficacy of supplements in reducing or preventing CVD or cerebrovascular events show mixed results.[57–60] In a recent meta-analysis that included various subgroup analyses, Myung et al.[60a] found no evidence that the use of vitamin or antioxidant supplements were helpful in either the primary or secondary prevention of CVD.

Although the available evidence may be ambiguous and sometimes conflicting, providers should work with their patients as they make decisions regarding dietary supplements, be aware of resources that are reliable in order to evaluate the supplements in use or being considered, and should routinely ask about the use of dietary supplements in a nonjudgmental fashion because some women will not disclose their use because of fear of a negative response[61] (Table 20.4). Most supplements and their safety and/or purported efficacies are associated

TABLE 20.4 Sources for Dietary Supplements

Organization	Online Website
American Botanical Council	http://www.herbalgram.org
Consumer Labs	http://www.consumerlabs.com
Health Canada	http://www.hc-sc.gc.ca
National Center for Complementary and Alternative Medicine (NCCAM)	http://www.nccam.nih.gov
National Nutritional Foods Association—Good Manufacturing Practices (GMP)	http://www.nnfa.org
National Sanitation Foundation International (NSF)	http://www.nsf.org/consumer/dietary_supplements/index.asp?program=DietarySup
Natural Medicines Comprehensive Database	http://www.naturaldatabase.com
Natural Standard	http://www.naturalstandard.com
Office of Dietary Supplements (ODS) National Institute of Health (NIH)	http://www.ods.od.nih.gov/index.aspx
U.S. Government Food and Drug Administration—GRAS (Generally Recognized As Safe)	http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm
United States Pharmacopeia (USP)	http://www.usp.org/USPVerified/dietarySupplements/

with evidence that is conflicting, uncertain, or insufficient. Providers should counsel patients about this and the possible impact of unknown quality of the supplements should be emphasized, particularly because lack of regulatory reform in the supplement industry in the United States makes it impossible to make an informed recommendation for specific brands. Clinicians and patients should also be aware that the use of herbs and dietary supplements alone or concurrently with medications may increase the risk of adverse events. Herbs and supplements with St. John's wort, magnesium, calcium, iron, and ginkgo appear to have the greatest number of reported interactions with medicines.[62] Among medications, those that affect the CNS or the cardiovascular system, as well as warfarin, insulin, aspirin, digoxin, and ticlopidine have the greatest number of reported interactions with herbs and supplements. Flaxseed, echinacea, and yohimbe have the largest number of documented contraindications. Most of these adverse interactions are due to altered pharmacokinetics, particularly when the metabolism of cytochrome P450 enzymes is involved. There are some commercial applications and software programs available that will allow clinicians to analyze a patient's entire drug and natural product usage to identify potential interactions.

OTHER SYSTEMS OF MEDICAL AND HEALTH CARE

Homeopathy

As a system of medicine, homeopathy differs entirely from the allopathic medicine traditionally practiced in Western civilization and, thus, has an entirely unique theoretical basis. In homeopathy, illness is perceived to be the organism's attempt to heal itself. Homeopathic remedies therefore are chosen to fit the illness as closely as possible and are used in the smallest possible dose. Homeopathic remedies are designed to stimulate a self-healing mechanism, not to correct a specific abnormality. One of the more controversial tenets held by homeopathy is that the smaller the dose of the treatment substance, the more potent its effect.

Homeopathic remedies are derived from substances that come from plants, minerals, or animals, such as the mountain herb arnica, crushed whole bees, and stinging nettle. The remedies may be in the form of sugar pellets, ointments, gels, drops, creams, and tablets. The FDA approaches homeopathic products, unlike botanical supplements, as over-the-counter drugs and regulates them as such. It does not evaluate them for safety or efficacy. Treatments are individualized so different people with the same condition may receive different therapies.

Homeopathy is a controversial topic in complementary medicine research. A number of the key concepts of homeopathy are not consistent with fundamental concepts of chemistry and physics. Another challenge is that because the treatments are so highly individualized, there is no uniform prescribing standard for homeopaths. Although many homeopathic remedies are highly diluted, some that are sold may not be and may contain high levels of active ingredients. This may lead to adverse side effects or drug interactions. Highly diluted treatments taken under the care of trained homeopathic professionals are generally safe. For some patients, a temporary worsening of symptoms may occur after taking a homeopathic treatment.

Licensing regulations for homeopathy vary among states; if a practitioner is licensed to practice medicine or another health care profession, they may usually practice homeopathy although in some states, nonlicensed professionals may also practice homeopathy.

Energy Medicine

Energy medicine is a modern term for the ancient idea of the vital life force that can be manipulated to produce healing effects and is rooted in traditional medical practices such as Ayurveda and Chinese medicine. Like some other CAM approaches, energy medicine approaches do not fit into the traditional allopathic model well, although there are efforts to understand and describe where and how they may interface with conventional Western medicine.[63,64]

Energy medicine encompasses two types of energy: measurable or veritable energy, and putative energy which as yet cannot be measured. Veritable energy sources include sound (vibrations), electromagnetic forces such as light, magnetism, and monochromatic radiations (e.g., laser), and other forms of wavelengths and frequencies. Putative energy, or biofields, are based on the concept that humans emit and are infused with a subtle form of energy yet to be measured. Some examples of energy medicine include intercessory prayer, Reiki, healing touch, tai chi, acupuncture, Qigong, sound and light therapies, and yoga. Practitioners of energy medicine believe that an energy body exists that has a direct influence on health and illness results from imbalances in the biofield(s).

The body emits and is influenced by energy. Biologic organisms are known to emit different quantities of light energy or biophotons.[65] However, there is not a single scientifically valid theory of how energy therapies work although multiple mechanisms have been proposed. While not consistently found, there is evidence of a direct effect of biofield-based therapies on cellular signaling mechanisms, as well as how human bioelectromagnetic energy may interact with known biochemical and physiologic systems, including the immune system.[66–69]

Research into the effectiveness of these modalities is increasing and has shown some consistently similar benefits.[70,71] A small randomized study of community-dwelling adults found significant reduction in measures of pain, depression, and anxiety in those who received Reiki treatments.[72] Patients' use of these modalities is increasing in hospital and clinic settings.[73] In general, these modalities are quite safe and there are no reports

TABLE 20.5 Web Resources for Energy-Based Treatment Modalities

Alternative Medicine Foundation	http://amfoundation.org/energywork.htm
Association for the Scientific Study of Consciousness	http://assc.caltech.edu/
Institute of Noetic Sciences	http://www.noetic.org/
International Society for the Study of Subtle Energies and Energy Medicine	http://www.issseem.org/
Society for the Anthropology of Consciousness	http://sunny.moorpark.cc.ca.us/_jbaker/sac/home.html
Samueli Institute for Information Biology	http://www.siib.org

of significant morbidity or mortality. It is not uncommon for intense emotions to arise during therapeutic sessions, so many providers suggest they be used with caution in people with psychoses. Some patients may feel slightly worse before they begin to feel better. Table 20.5 includes a list of Web resources that patients may find helpful.

Naturopathy

Naturopathy is a medical system based on the principle *Vis Medicatrix Naturae*, or the healing power of nature. It is based on principles that recognize the innate healing capacity of the body, emphasizes disease prevention, and encourages individual responsibility in achieving and maintaining optimal health. Treatment focuses on the underlying condition and not the individual symptoms. Naturopathic practitioners follow a specific but adaptable therapeutic order of interventions, starting with the most minimal and escalating to higher levels of interventions as necessary (Table 20.6).

Naturopaths practice as primary care providers and use natural medicines and interventionist and CAM therapies as needed. Naturopaths are trained over a period of 4 years at accredited doctoral-level naturopathic medical schools (http://www.naturopathic.org). They may choose to specialize in certain populations or certain modalities, for example, botanical medicine. Commonly, an informal practice of mentorship occurs after graduation; there are a limited number of postdoctoral Council on Naturopathic Medical Education (CNME)-certified naturopathic residency programs. Naturopaths are trained as primary care physicians with an emphasis in natural medicine, commonly in ambulatory settings. They obtain histories, provide physical examinations, and may order laboratory and diagnostic testing as well as diagnostic imaging services. Depending on the state, they may be licensed to perform minor procedures, administer vaccines, and prescribe medications. Many see naturopathic physicians for the same conditions for which they see conventional providers, for example, fibromyalgia and other forms of chronic pain, otitis media, depression, low back pain, and there is evidence for the efficacy of naturopathic treatments in these and other conditions.[74–78]

TABLE 20.6 Naturopathic Therapeutic Order

1. Establish the conditions for health
   - Identify and remove disturbing factors
   - Institute a more healthful regimen
2. Stimulate the healing power of nature (vis medicatrix naturae): the self-healing processes
3. Address weakened or damaged systems or organs
   - Strengthen the immune system
   - Decrease toxicity
   - Normalize inflammatory function
   - Optimize metabolic function
   - Balance regulatory systems
   - Enhance regeneration
   - Harmonize life force
4. Correct structural integrity
5. Address pathology: use specific natural substances, modalities, or interventions
6. Address pathology: use specific pharmacologic or synthetic substances
7. Suppress or surgically remove pathology

From Zeff J, Snider P, Pizzorno JE. *Textbook of Natural Medicine*. 3rd ed. St. Louis, MO: Elsevier; 2006, with permission.

Ayurveda

The term "ayurveda" means "the knowledge of life" and involves restoring balance to the mind, body, and spirit.[79] Without this balance, wellness is impossible and true health is only possible when one is balanced and centered. Ayurvedic medicine is one of the world's oldest medical systems and originated in India, where it evolved over thousands of years, and is still actively used by over 80% of the population, either alone or in combination with Western medicine. It is also used in Bangladesh, Sri Lanka, Nepal, and Pakistan. Ayurveda is based on concepts around universal interconnectedness, the body's constitution (prakriti), and life forces (doshas). In Ayurveda, all things in the Universe, both living and nonliving, are joined together and a person's health is good if his or her mind and body are in harmony and if the individual's interactions with the universe are natural and wholesome. Disease occurs when a person is out of harmony with the universe; disruptions in harmony may be physical, emotional, spiritual, or a combination of the three.

Ayurveda also focuses on a body's constitution (prakriti) or general health, the likelihood that the body will become out of balance, and the body's ability to recover its balance or health. Each person has a unique prakriti, reflective of his or her physical and psychological characteristics and how his or her body functions in maintaining health. The prakriti is not believed to change over a person's lifetime. Major characteristics of the prakriti are three life forces or energies, called doshas, and these control the activities of the body. The doshas are known by their original Sanskrit names: vata, pitta, and kapha. A person's likelihood of developing certain diseases is thought to reflect how his or her doshas are

balanced, as well as the overall state of the physical body, the person's mental health, and lifestyle factors as well.

Each dosha is made up of two of five basic elements (ether, air, fire, water, and earth) and each dosha has a specific relationship to bodily functions. Individuals are a unique combination of the three doshas, although one dosha usually predominates. Doshas are constantly being formed and reformed by activity, food, and bodily processes. Each dosha has unique psychological and physical characteristics, and an imbalance of a dosha will produce symptoms unique to that dosha.

Ayurvedic practitioners determine a person's primary dosha and the balance of his or her doshas through historical questioning; a detailed physical exam; and checking the patient's urine, stool, speech and voice, and pulse. Ayurvedic treatments involve dietary changes, various botanicals, massage, meditation, yoga, and other lifestyle measures tailored to a person's "dosha" and his or her current state of health. Treatments rely heavily on herbs and other plants, including oils and spices. Plant compounds are grouped into categories according to their effects. The goal of these treatments is to eliminate impurities (panchakarma), reducing symptoms, increasing resistance to disease, and reducing worry and increasing harmony. The patient must take an active role in his or her treatment because many Ayurvedic therapies require changes in diet, lifestyle, and habits.

Training to be an Ayurvedic practitioner may take 5 years or longer and students may earn either a bachelor's degree (Bachelor of Ayurvedic Medicine and Surgery, or BAMS) or a doctoral degree (Doctor of Ayurvedic Medicine and Surgery, or DAMS).

There is evidence of increasing acceptance of Ayurveda and some treatments are being incorporated into mainstream medicine.[80] Concerns have been raised about the safety of Ayurvedic Indian-manufactured patent medicines and herbs containing toxic compounds and heavy metals such as lead, mercury, and arsenic.[38,81]

Traditional Chinese Medicine

Traditional Chinese medicine (TCM) developed more than 2000 years ago, but it has undergone significant changes and developments over the centuries. New ideas have been embraced and old ones discarded as new technologies, information, and even exposure to other medical systems have been introduced. As a result, conflicting concepts of disease etiology, methods and systems of diagnosis, and treatment are juxtaposed in Chinese medicine, and the clinician relies on the perspective he or she believes to be the most applicable.

TCM views human beings as being interconnected with nature and subject to its forces. Within the body, the various tissues and organs are functionally interconnected and the state(s) of health or disease of a person depends on the balance of these interconnected functions. TCM focuses primarily on body functions, and not so much anatomical structures.

The key components of the TCM theoretical framework include the following:

- Yin and Yang: These are opposing but complementary forces that shape the world and all of Life;
- Meridians: These are the pathways through which the body's vital energy or life force, qi or ch'i, circulate through the body; the circulation of qi must be maintained in balance and harmony if health is to be achieved. TCM recognizes several different kinds of qi.
- Eight principles and five phases or elements: There are eight principles used to evaluate symptoms and categorize conditions: heat/cold, exterior/interior, deficiency/excess, and yin/yang. The five elements (wood, water, metal, earth, and fire) explain how the body works and correspond to particular organs and tissues in the body.

Treatment in TCM is individualized. The practitioner will attempt to determine the nature of the imbalance through inspection, focusing on the face and the tongue, auscultate and listen for particular sounds, actively smell and attend to the patient's body and breath odor, palpate the body for tender points and palpate a variety of pulses as well as the abdomen and ask the patient about a variety of symptoms such as chills, fever, appetite, taste, etc. TCM therapies include Chinese herbal medicine, acupuncture, moxibustion, cupping, Chinese massage, Qigong and tai chi, and dietary therapy, to list a few. If herbal medicine is determined necessary, a batch of medicinals is prepared as a decoction of 9 to 18 substances. Plant elements and extracts are the most commonly used components. There are over 13,000 medicinals used in China and over 100,000 medicinal recipes recorded in ancient literature.

Most U.S. states regulate the professional practice of TCM and most license acupuncture. The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) has separate certification programs in acupuncture, Chinese herbology, and Oriental bodywork and administers a national written exam that many licensing state require practitioners to pass for licensure.

While herbology is a mainstay of TCM, another common practice is the use of acupuncture. Traditional acupuncture, which is defined as needling insertion, moxibustion thermal stimulation, and cupping techniques at acupuncture points, has become popular in the United States and in 2008, the NIH reported that 3.1 million American adults and 150,000 children used acupuncture in 2007.[1,82]

Acupuncture involves placing hair-thin metal needles through the skin at specific points on the body to relieve pain and promote well-being. The needles are placed along meridians or at tender points in an effort to promote or unblock the flow of qi. The needle is manipulated until either the physician perceives that the needle is being grabbed by the tissues or the patient experiences *de qi*, a sensation described as a mix of heaviness, soreness, distention, tingling, and numbness that may travel from one place to another. Patients then lie still

for 20 to 40 minutes, with the needles in situ. Heat and electric stimulation may be used to augment the needling sensation. Acupuncture treatment typically involves 10 sessions, although this varies, depending on the reason for its use. Most patients report acupuncture as relaxing and calming.[83]

The exact mechanism(s) of action for acupuncture are not fully understood. There does appear to be an analgesic effect mediated in part by endogenous opioid release, there may be some modulation of the limbic system, and there may be local tissue responses that help to decrease inflammation.[84–87] Thousands of trials have been conducted using acupuncture for a wide diversity of conditions but there are challenges in methodology when evaluating acupuncture, particularly with regards to what serves as a control, or appropriate placebo.[88] There is clear evidence for clinically relevant, and comparable, effects of acupuncture compared to standard care or enhanced standard care for low back pain, knee osteoarthritis, neck pain, and headaches.[89–92] In the United States, back pain is the most common reason for visits to acupuncturists and, interestingly enough, are one of the major reasons patients are seen in the primary care setting (the other most common complaints are knee pain, other musculoskeletal problems, and respiratory issues).[74,93] The effects of acupuncture appear to last over a long time period, that is, 6 months or possibly more. In the United States, physician acupuncturists are predominantly primary care physicians, although anesthesiologists and pain management specialists also make up significant proportions of practitioners.[94] Acupuncture training programs are certified by the American Board of Medical Acupuncture and each program requires at least 300 hours of training, with one-third being involved in acupuncture-specific training (see Table 20.7 for Internet resources related to acupuncture).

Given that millions of acupuncture procedures are done annually, serious adverse events are uncommon, particularly if they are done by licensed, qualified practitioners but even so, any medical intervention may cause damage and this must be considered and included when counseling patients.[1,95] For the years 2000 to 2011, a total of 117 reports containing 308 adverse events associated with acupuncture (294 cases), moxibustion (4 cases), and cupping (10 cases) were identified from 25 countries and regions.[96] Infections included mycobacterial, staphylococcal, and other causative organisms. A total of 239 reported cases were infections associated with acupuncture in 17 countries and regions. Most of the infections seemed to come from unsterilized equipment and poor hygienic conditions. All other cases recovered after the infection was treated. There were 38 cases of organ or tissue injuries, 13 were pneumothoraxes, 9 involved the CNS, 4 were peripheral nerve injuries, 5 were heart injuries, and 7 were other organ and tissue injuries.[96] Adverse events reported with moxibustion included bruising, burns and cellulitis, spinal epidural abscess, and large superficial basal cell carcinoma. Associated injuries with cupping include keloid scarring, burns, and bullae.

TABLE 20.7 Acupuncture Internet Resources

Acupuncture information for patients: National Center for Complementary and Alternative Medicine	http://nccam.nih.gov.ezproxyhost.library.tmc.edu/health/acupuncture/
Acupuncture training programs for physicians: American Academy of Medical Acupuncture	http://www.dabma.org/programs.asp
Acupuncture Education International	http://jefferson.studioabroad.com/index.cfm?FuseAction=Programs.ViewProgram&Program_ID=36493

INTEGRATIVE THERAPIES FOR COMMON PROBLEMS IN WOMEN

Premenstrual Syndrome

Premenstrual syndrome (PMS) is a common problem in women (see Chapter 8 on Premenstrual Syndrome and Premenstrual Disphoric Disorder). Many conventional remedies are given to women with PMS including selective serotonin reuptake inhibitors (SSRIs), nonsteroidal anti-inflammatory drugs (NSAIDs), birth control pills, anxiolytics, and spironolactone. Smoking cessation and decreased caffeine intake have been linked to fewer PMS symptoms.[97] Dietary manipulation is often used in PMS, but there are no randomized controlled trials to prove their beneficial effects. A diet high in fiber and soy and low in animal fat has been help to control estrogen levels and so is often recommended to help control symptoms, although its true efficacy in controlling PMS symptoms remains unproven.[97] Good evidence has shown that routine exercise, especially aerobic activities, is helpful as well.[98]

A variety of nutritional approaches have been tried with PMS. In a large multicenter trial, women receiving 1200 mg of calcium carbonate daily during the luteal phase reported a 48% reduction in symptoms.[99] Vitamin B6 at doses of 50 to 100 mg daily has been recommended for the treatment of PMS, but the results of some trials have been mixed.[100,101] Supplementation with vitamin E at doses of 150 to 600 IU daily has shown some promising results, but the studies were small or had methodological problems.[100,102] The use of supplemental magnesium has had mixed results.[100,102]

Chasteberry (*Vitex agnus-castus*) has proved to be effective for treating PMS symptoms in several trials.[100,103] It was shown to be equal to fluoxetine in efficacy of reducing PMS symptoms in a double-blind, placebo-controlled trial.[104] Recommended dosing is 500 mg one time daily. The German Commission E (the German equivalent of the U.S. Food and Drug Administration) approved chasteberry for the treatment of PMS and mastalgia. The potential exists for drug–herb interactions with dopamine antagonists, and this herb has not been shown to be safe during pregnancy and is contraindicated in lactating women.[105]

Black cohosh (*Cimicifuga racemosa*) is widely used for menopausal symptoms, may have some mild SSRI activity, and may be best for women who have depressive symptoms in the premenstrual period.[106] Dosing is 20 to 40 mg of the standardized extract two times daily. Black cohosh is generally thought to be safe, but there have been a few case reports of liver damage in patients who took it. Although no causal relationship was established, monitoring liver function during treatment is recommended.[107]

Evening primrose oil (*Oenothera biennis*) has been used for PMS symptoms, but there is no evidence that it is effective.[108]

St. John's wort (*Hypericum perforatum*) is frequently used to treat depression and has also been used with mixed results for treatment of anxiety and depressive symptoms in PMS.[109,110]

Menopause

Physicians must recognize that menopause is a normal transition in life and not a disease. Women experience menopause differently in many cultural and personal ways, and generalizations should be avoided. Symptoms of menopause tend to include hot flashes, emotional lability, "brain fog," and vaginal dryness among others. Treatment should be tailored to specific symptoms experienced by individual patients rather than just as treatment of a perceived "estrogen deficiency."

The risks and benefits of hormone replacement therapy should be considered carefully prior to recommending treatment for individual patients. Because some patients may ask their physicians for bioidentical hormones, it is helpful to understand the term. Bioidentical hormones have exactly the same structure as endogenous human hormones. The terms "natural" and "synthetic" refer to the source of the hormone, not the structure. Conjugated equine estrogens, which come from pregnant mares, and phytoestrogens found in soy products are natural, but they are not bioidentical. Estradiol can be synthesized from soy beans is not natural but it is bioidentical. Bioidentical hormones can be obtained with a traditional prescription and from custom compounding pharmacies. There is no evidence that bioidentical or compounded hormones are safer than conventional hormone therapy.[111] Bioidentical estrogen products that are commonly available by prescription include Estrace, Climara, Vivelle, Estring, Vagifem, Activella, and Estraderm, among others. Bioidentical micronized progesterone is available as Prometrium by prescription. The bioidentical hormones that are available by prescription from traditional pharmacies have the added benefit of being covered by most prescription insurance plans, which is not always the case with compounded prescriptions.

Some practitioners and some compounding pharmacies use salivary levels of hormones to individualize hormone prescriptions for women, but this method has not been studied adequately in menopausal women.[112] It is better to use the patient's individual response to therapy as a guide for dosing hormone replacement therapies.

The benefits of exercise are well established at all ages, and this is especially true for the menopausal transition period. Women who exercise can have increased bone density, decreased body fat, increased muscle mass, and an improved sense of well-being.[113,114] A recent Cochrane review failed to find a significant decrease in hot flashes in women who exercise.[115] Increased dietary consumption of soy products, especially miso and tempeh, has often been recommended as a remedy for hot flashes. Although recent reviews of the evidence have shown some trends toward a benefit, none contain conclusive evidence that soy consumption reduces the incidence of vasomotor symptoms.[116–118] Of course, all patients should be encouraged to consume a healthy diet that is low in saturated fats and high in fruits, vegetables, and unprocessed grains that can include soy products.

Concerns about bone density arise in the perimenopausal and postmenopausal periods. Checking serum vitamin D levels is recommended to help guide supplementation recommendations for individual patients.[119] Normal levels of 25, cholecalciferol range from 30 to 80 ng/mL, but most nutrition experts recommend at least 40 ng/mL. Most women can take 1000 IU vitamin D3 daily with good effect. Oversupplementing vitamin D is to be avoided because of the possibility of increased fractures and increased calcification of arterial plaques. Studies on calcium supplementation and bone density have been variable; however, when compliance is controlled, as in institutionalized patients, osteoporotic fractures are reduced significantly.[120] Postmenopausal women should take approximately 1000 to 1500 mg of calcium daily, which has been shown to decrease the rate of bone loss. Calcium citrate is more easily absorbed, contains fewer contaminates (e.g., lead and aluminum), and so should be the supplement that physicians recommend.[121]

Phytoestrogens are plant-derived compounds that may display estrogenic and antiestrogenic effects. The three major classes of phytoestrogens include isoflavones, lignans, and coumestans. Isoflavones are in high concentrations in soybeans, soybean products, and red clover. Two types of isoflavones, genistein and daidzein, are thought to be the most potent estrogens of phytoestrogens, although they are weaker than human estrogens. These are found in soybeans, chickpeas, and lentils. Lignans are primarily found in flaxseed as well as in lentils, grains, fruits, and vegetables. The amount of phytoestrogen found in any plant varies, depending on the location of the crop, time of harvest, and processing techniques used. The bioavailability of phytoestrogens in humans depends on the intestinal microflora. Although there have been multiple trials looking at the efficacy of isoflavones in treating menopausal symptoms, collectively they fail to conclusively demonstrate their superiority over placebo.[122–124]

Black cohosh is frequently used for menopausal symptoms, but studies have had mixed results. One systematic review of randomized clinical trials determined that this substance produced a combined estimate of about 26% reduction in vasomotor symptoms compared with placebo.[125] In the Herbal Alternatives for Menopause Trial (HALT), 351 symptomatic perimenopausal or postmenopausal women were randomly assigned to one of five possible interventions: black cohosh only, a multibotanical regimen with black cohosh in it, the multibotanical regimen and counseling about increasing dietary soy, conjugated estrogen 0.625 mg with or without medroxyprogesterone acetate, or placebo.[126] After 1 year, the women in the estrogen group showed significant reduction in hot flashes compared to placebo. There was no significant reduction in any of the herbal interventions, and the effect of increasing soy intake could not be assessed because too few women reached the target goal.

A few cases of presumptive herb-induced liver failure have been reported in women taking black cohosh, so its use should be discouraged by patients with known liver disease, and liver function should be monitored in those taking this botanical supplement.[127] Although black cohosh is certainly not as effective as estrogen for menopausal symptoms, it has a relative beneficial risk/benefit profile and is certainly worth a try for many patients. The recommended dosing is 40 to 80 mg per day.

Red clover (*Trifolium pratense*), used for menopausal symptoms in several studies, has had conflicting results.[128] Red clover is relatively safe and the isoflavones in it may have phytoestrogenic effects that are similar to those in soy. It is usually taken as a tea, two to three cups a day, or in a capsule form containing 40 mg isoflavones, two to three times daily.

Ginseng root contains a subtype of isoflavone, a type of phytoestrogen. In a placebo-controlled multicenter randomized trial of 384 menopausal women, there was no significant effect in reducing the frequency of hot flashes after 4 months, although there seemed to be a favorable effect on psychological well-being, a finding found in other, but not all, studies.[129–132] Its use is not recommended in the presence of breast cancer because there have been case reports linking its use with postmenopausal bleeding as well as potentiating the effects of warfarin.[133,133a]

St. John's wort may be helpful in treating mood swings, and doses of 1800 mg per day have been shown to be as effective as SSRIs in treating depression.[134] Other studies have been mixed, and the results of this study may reflect the relative ineffectiveness of traditional SSRIs rather than the efficacy of St. John's wort. The physician must take care to guard against serotonin syndrome and other possible drug–herb interactions.

Grape-seed oil has benefit as a vaginal lubricant to assist women with vaginal dryness in the perimenopausal and postmenopausal periods.

Mexican wild yam (*Dioscorea villosa*) contains a progestin; however, this form of progestin cannot bind to human progesterone receptors and, thus, has no biologic activity for humans.

Maca root (*Lepidium peruvianum*) in one small, randomized, double-blind, placebo-controlled, crossover trial was found to reduce anxiety and depression and to lower sexual dysfunction in postmenopausal women.[136] Maca is commonly dosed at 500 mg three times a day of dried root powder in capsules.

Acupuncture has been studied for ameliorating hot flashes but results have not been promising. In a meta-analysis of five trials using sham acupuncture as the control, there were no significant differences between the groups in severity or frequency of hot flashes.[137]

Vaginitis

Boric acid, dosed in a 600-mg gelatin capsule, inserted into the vagina daily for 2 weeks had a higher cure rate in diabetic women with vaginal candidiasis than did a single dose of fluconazole.[138] It also has shown evidence of efficacy in recurrent vulvovaginal candidiasis, particularly in instances of non-albicans *Candida* spp. infections.[139] Very little absorption occurs and, thus, the chance of toxicity is small. Boric acid has rarely been associated with vaginal discomfort, should not be used in pregnancy, and has the added benefit of being very inexpensive.

Tea tree oil (*Melaleuca alternifolia*) vaginal suppositories have been recommended for the treatment of vulvovaginal candidiasis and bacterial vaginosis, but the literature to support their use is scant.[140] This oil is usually inserted intravaginally for six nights.

The evidence for probiotics treatment of vaginitis and vaginosis is mixed. In a double-blind randomized clinical trial of 120 Chinese women aged 18 to 55 years with two or more documented episodes of bacterial vaginosis (BV) in the past year, use of vaginal suppositories containing *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, and *Streptococcus thermophilus* each day for 1 week, followed by a week off, and then a final week of daily use showed fewer recurrences of BV over the next 2 months than those who used placebo.[141] Significantly, fewer women who used the suppositories reported recurrences in phone interviews 2 to 11 months after treatment as well. A Cochrane review did not find sufficient evidence for or against the use of probiotics as a treatment for BV.[142]

Cancer

The use of complementary therapies is common among cancer patients and survivors, and one study showed that the therapies used most often were prayer and spiritual practice, relaxation, faith and spiritual healing, and nutritional supplements and vitamins.[143] The Office of Cancer Complementary and Alternative Medicine (OCCAM) within the National Cancer Institute (NCI) at the NIH offers a wide variety of evidence-based summaries, toolkits for talking with patients about their use of CAM, links to CAM resources, and a list of integrative

medicine programs and more on their website, www.cam.cancer.gov.

Diet can influence cancer outcomes. Selected vegetables and herb mix (SV) is a blended, boiled, and freeze-dried product containing ingredients with purported immunostimulatory and anticancer properties. In two studies of patients with non–small cell lung cancer, prolonged survival was noted in patients who used SV daily.[144,145] Further research is underway.

Good evidence suggests that nutrition has an impact on both cervical and breast cancers. One study showed as much as a 60% risk reduction for development of cervical cancer in women who have more dietary intake of fiber; vitamins C, E, and A; alpha/beta carotene; lutein; folate; and total fruit and vegetable intake.[146] Friedenreich and Cust[147] have shown that physical activity can reduce the risk of breast cancer by about 20 to 30%. We have no convincing evidence that changing dietary patterns is helpful after the diagnosis of breast cancer; however, evidence does show that maintaining a healthy body weight is helpful for prevention of breast cancer.[148] A curious finding is that even though women can reduce their risk of breast cancer with lifestyle changes, women with a family history of breast cancer do not routinely make those changes.[149] Exercise, yoga, stress reduction, and social support have all been shown to be beneficial during and after treatment for breast cancer.[150]

Trials attempting to elucidate the role of vitamin D in breast cancer continue to be inconsistent.[151] Green tea has shown benefit in arresting cell growth, increasing apoptosis of cancer cells and decreasing the production of epidermal growth factor receptor.[152] Many integrative medicine providers recommend consumption of at least six cups of green tea daily for patients with cancer. Turmeric (*Curcuma longa*) can induce apoptosis, reduce tumor cell invasion and metastasis, and numerous studies have failed to show toxic side effects.[153] Turmeric extract is generally dosed at 500 mg three times daily.

TCM is increasingly being used in the West for cancer patients and plays a role in reducing the side effects of conventional therapy and improving quality of life.[154] In a review of controlled clinical studies published in Chinese involving 2385 randomized controlled trials and 579 nonrandomized trials, the majority of studies (72%) combined TCM with conventional therapy.[155] Herbal medicine was the most frequently used TCM modality (90%). Other modalities included acupoint stimulation, dietary therapy, massage, Qigong, TCM five-element music therapy, and TCM psychological intervention. In the herbal therapies used, most were decoctions and over half were individualized. In the aforementioned review, TCM had a higher impact on preventing relapses/metastases; hemorrhage; radiation-induced injury; nausea, vomiting, and gastrointestinal issues; and chemotherapy side effects when compared to treatment of the cancer per se.

Ginger is effective as an antiemetic and may be helpful as an adjunct in patients with chemotherapy-associated nausea.

Johnston et al.[156] found that cancer-related fatigue showed a significant decline after patients followed structured educational programs and received a series of acupuncture treatments. Several other studies showed similar results and acupuncture is thought to be a very safe healing modality, so its use for cancer-related fatigue should be recommended routinely.[157–159] Massage is another safe modality that has been shown to be effective in reducing cancer-related fatigue[160] and may also be helpful in reducing both physical and emotional discomfort related to stressful health conditions.[160,161]

Urinary Tract Infections

Urinary tract infections (UTIs) are common in women, and recurrent treatment of UTIs with antibiotics can lead to antibiotic resistance. Several natural approaches may be taken to prevent and to treat the common UTI. Cranberry (*Vaccinium macrocarpon*) extracts, pills, and juices have been well studied and have been shown to be effective in preventing UTIs in elderly women[162] and in sexually active women of all ages[163] but not to be helpful for prevention in patients with neurogenic bladders.[162–164] Capsules containing cranberry are generally tolerated better than the large quantity of juice that must be consumed to be effective. They are usually dosed at 200 to 500 mg three times daily. Uva ursi (*Arctostaphylos uva-ursi*) has been shown by the German Commission E in in vitro studies to be active against *Escherichia coli*, *Proteus vulgaris*, *Ureaplasma urealyticum*, and *Staphylococcus aureus*.[165] In one small randomized controlled trial performed in the 1990s in women who had at least three UTIs in the preceding year, Uva ursi was found to decrease the rate of recurrence.[166] Of note, Uva ursi has been associated with eye complications, so it should not be used for long-term UTI prophylaxis. In a review of the literature on natural approaches for UTI, cranberry and probiotics were found to be effective and safe for long-term prevention.[167]

HEALTHY AGING

Aging is neither an illness nor a pathologic condition. As Mackenzie and Rakel[168] state, "Being born sets the aging process in motion and only death can stop it. Our goals, as health professionals, should be to extend life while enhancing the quality of life by preventing disease when possible and otherwise by managing it optimally." Patients should be helped to live full, active, and healthy lives, regardless of their age. At all stages of the life cycle, incorporating healthy foods, regular exercise, mind–body practices, and spiritual and social connection as well as appropriate preventive and screening measures should be encouraged. Providers are important role models for our patients and communities and as such should proactively incorporate healthy lifestyle and stress management into their own lives.

CLINICAL NOTES

- Complementary and alternative healing modalities are used frequently by our patients and physicians should address these issues with a nonjudgmental attitude and encourage patients to seek information from reliable resources.
- Nutrition and physical activity are paramount in promoting wellness and preventing illness.
- Mind–body interventions are the key to helping our patients reduce stress and improve their sense of well-being.
- Several healing systems have very different frameworks from our Western allopathic system. Homeopathy, Ayurveda, and traditional Chinese medicine are ancient systems of healing that offer many benefits for interested patients.
- Manual medicine and energy medicine modalities can be helpful for many patients and have been shown to be safe and effective for many musculoskeletal problems.
- Help patients choose high-quality, safe, and effective dietary supplements, so that they do not have to rely on the health food store clerks for medical advice.
- Safe, natural, and effective remedies are available for many common problems experienced by women. These should be appropriately incorporated into their care.
- Curing is not always possible. Healing is always possible.
- When a medical encounter is focused on the whole patient, a truly healing relationship becomes possible. In this relationship, the patient is central, and her doctor acts as a guide, advisor, or consultant.

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CHAPTER 21

Diagnosis and Management of Hereditary Cancer

Monique A. Spillman and Andrew Berchuck

Most cancers arise due to accumulation of genetic alterations in several genes involved in cell growth and DNA repair. In contrast to "sporadic" cancers, in which all mutations are acquired, hereditary cancers arise in individuals who have inherited a mutation in a cancer-causing gene. These individuals generally develop cancer at a younger age than sporadic cases, may develop multiple tumors in a single organ, or have bilateral development of tumors in paired organs and they often develop multiple primary cancers of different types. Other characteristics that may raise suspicion of a familial form of cancer susceptibility include a family history of cancer of the same type or related type in one or more first-degree relatives, a high rate of cancer in the family, or cancer occurring in an individual or with a family with congenital anomalies or birth defects. Several hereditary cancer syndromes have been identified and are characterized by clustering of specific types of cancers within families. An online catalog of cancer family syndromes is available at www.ncbi.nlm.nih.gov in the Online Mendelian Inheritance in Man (OMIM) database.

Malignancies of the colon, breast, and ovary are the most common hereditary cancers in women, and approximately 5 to 10% of these cancers have a strong hereditary basis. In the 1990s, many of the genes responsible for high-penetrance hereditary cancer syndromes were identified, and this has facilitated genetic testing and clinical interventions aimed at decreasing cancer mortality.[1–3] With the availability of genetic testing, cancer prevention and early detection efforts can be focused on mutation carriers. Noncarriers in these families can be reassured they are not at greater risk than the general population. This chapter summarizes progress to date in the diagnosis and management of hereditary cancer syndromes.

BASIC CANCER GENETICS

Cancer is a disease in which there is loss of growth regulatory control, allowing unrestrained proliferation of tumor cells. Normal cellular proliferation is regulated by complex molecular pathways that contain numerous checks and balances. *Oncogenes* encode proteins that stimulate proliferation, whereas *tumor suppressor genes* encode proteins that inhibit proliferation. In each organ, there is a carefully programmed balance between these opposing classes of gene products. In some organs, such as the bone marrow, the genetic program allows for constant proliferation and regeneration of the cellular supply; whereas in the brain, proliferation rarely occurs and the total number of cells is relatively static. Some of these oncogenes and tumor suppressor genes are also involved in regulating differentiation and apoptosis (programmed cell death), which are processes that also serve to control the population of cells within an organ.

Alterations in the genes that control cellular growth can cause malignant transformation. Oncogenes can be activated by several mechanisms. In some types of cancers, activation occurs by amplification of oncogenes (e.g., c-*myc,* HER-2/*neu*). Instead of 2 copies of one of these growth stimulatory genes, there may be as many as 40 copies. Some oncogenes may become overactive if affected by point mutations (e.g., K-*ras*). Finally, oncogenes may be translocated from one chromosomal location to another, and they may come under the influence of promoter sequences that cause overexpression of the gene (e.g., *abl*).

Loss of tumor suppressor gene function can also result in overactive proliferation and outgrowth of a tumor. This usually involves a two-step process in which both copies of a given tumor suppressor gene are inactivated. In most cases, mutation of one copy of a tumor suppressor gene occurs, along with complete loss of the other copy of the gene due to deletion of a large segment of the chromosome where the gene resides. Knudson[4] termed this process the "two-hit" hypothesis of cancer development. DNA repair genes play an important role in preventing the development of human cancers. Each time a cell divides, the DNA is copied so both cells will receive a complete set of the genetic code. Although DNA synthesis occurs with high fidelity, it is estimated that spontaneous errors (mutations) occur about once every million bases. In nondividing cells, mutations may arise due to endogenous processes such as DNA methylation and deamination. The cellular DNA repair systems are able to fix much of this genetic damage, but some mutations elude this surveillance system. The rate at which critical mutations occur in cells may be accelerated if

TABLE 21.1 Selected Hereditary Cancer Syndromes

Syndrome	Gene	Chromosome	Predominant Cancers
Familial breast/ovarian cancer	*BRCA1*	17q21	Breast, ovary
	BRCA2	13q12	Breast, ovary
	CHEK2	22q12.1	Breast
Ataxia-telangiectasia	*AT*	11q22	Breast
Hereditary nonpolyposis colon cancer (HNPCC)	*MSH2*	2p16	Colon, endometrium, ovary, and others
	MLH1	3p21	
	PMS1	2q31	
	PMS2	7p22	
	MSH6	2p16	
Familial adenomatous polyposis coli (FAP)	*APC*	5q21	Colonic polyps, cancer
Hereditary colon/stomach	*MYH/MUTYH*	1p34.1	Colon/stomach
Li-Fraumeni syndrome	*p53*	17p13	Sarcomas, leukemias, breast, brain, and others
Wilms tumor	*WT1*	11p13	Kidney
von Hippel-Lindau	*VHL*	3p25	Kidney and others
Neurofibromatosis	*NF1*	17q11	Neurofibromas
	NF2	22q12	Neurofibromas
Retinoblastoma	*Rb*	13q14	Retinoblastoma sarcomas
Familial melanoma	*MLM*	1p36	Melanoma
	CDKN2 (p16)	9p21	
Multiple-endocrine neoplasia			
Type 1	*MEN1*	11q13	Thyroid, adrenal, pancreas, pituitary, parathyroid
Type 2	*ret*	10q11	Thyroid, adrenal, parathyroid
Hereditary papillary renal carcinoma	*met*	7q31	Papillary kidney
Cowden disease	*PTEN*	10q24	Many

the DNA repair genes themselves have undergone inactivating mutations. In general, cancer occurs only after damage to several DNA repair genes and growth regulatory oncogenes and tumor suppressor genes.

Hereditary cancers arise due to an inherited mutation in one of the earlier mentioned classes of genes (see Table 21.1 for some selected hereditary cancer syndromes). Persons who inherit a mutation in a cancer gene carry that mutation in every cell of their body and have a strikingly increased lifetime risk of developing one or more cancers when the second copy of the gene is inactivated in a single cell. These cancers often develop at a younger age than would be expected, including in children. Some rare cancers in young children, such as retinoblastoma and Wilms tumor, result from inherited mutations in tumor suppressor genes.

PRINCIPLES OF CANCER GENETIC COUNSELING

Obtaining a thorough cancer history from the patient and/or the family is a vital first step in caring for families with hereditary cancer. The seemingly simple act of gathering information forms the foundation on which the rest of the process is based. The importance of careful documentation of family history, including review of clinical materials from other cancer cases in the family, has been stressed for many years by Dr. Henry T. Lynch, one of the pioneers of hereditary cancer genetics.[5] His own compulsively assembled pedigrees allowed him to define two familial cancer syndromes: Lynch I (colon cancer), and Lynch II (colon cancer and other cancers).[5]

Family history questionnaires administered in an office setting are an effective method of eliciting an initial family history.[6] A complete cancer family history should begin by ascertaining cancer information, including age of onset, and specific type of cancer in all first-degree relatives, including mother, father, siblings, and children. Data on second-degree relatives, including grandparents, aunts, and uncles, should also be obtained from *both* maternal and paternal sides. Family members without cancer should be included because their unaffected status can provide clues to the inheritance pattern. A family cancer history should ideally be obtained from more than one individual in families where there is a suspicion of a hereditary syndrome.[7] This information can be depicted diagrammatically in a pedigree (Fig. 21.1). To make a pedigree as accurate as possible, cancer diagnoses should be confirmed when possible by review of pathologic specimens or medical records.

Pedigrees concisely convey a large amount of information, including the presenting cancer case (proband), others with cancer, cancer decedents, and potential mutation carriers. Important additional information recorded includes the age of onset of cancers, second cancers, bilaterally of a cancer, stage of the cancer, and metastatic location. In addition, cancer histology, age of unaffected

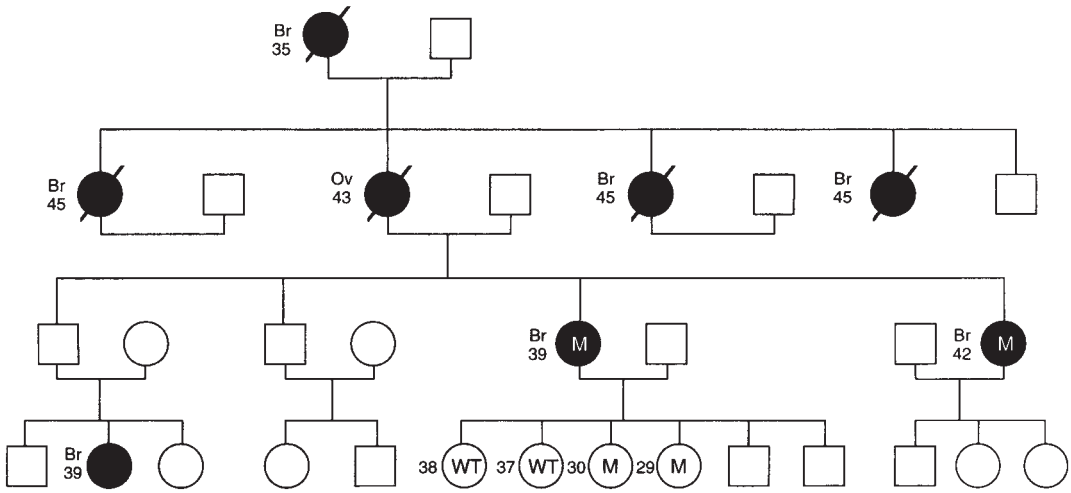

FIGURE 21.1 Familial ovarian cancer pedigree with *BRCA1* mutation. The ages of family members and types of cancer are noted. *Slashes* denote individuals who have died of cancer. Individuals denoted *M* are *BRCA1* mutation carriers, whereas individuals denoted *WT* have normal *BRCA1*. □, males; ○, females; ■, affected males; ●, affected females.

individuals, exposure to carcinogenic agents, suspected extended family history of cancers, and the pattern of cancer occurrence among generations is recorded.[8] A known genetic disorder in the family should be prominently noted because some syndromes also predispose individuals to cancers (e.g., Fanconi anemia, xeroderma pigmentosa, Bloom syndrome, ataxia-telangiectasia). In addition to family history, a complete personal history of potential cancer risk-modifying factors should be obtained, for example, hormone use, birth control pill use, menopausal status, diet, parity, breast-feeding history, and concomitant medical conditions.

An ethnic history should also be elucidated, especially for patients of Ashkenazi (Eastern and Central European, including Germany, Poland, Lithuania, Ukraine, and Russia) Jewish heritage. Specific mutations, called founder mutations, that are fairly common have been identified in various ethnic groups.[9] It is thought that founder mutations arose many generations ago in a single individual and later became more prevalent, perhaps because the ancestral groups was once geographically or culturally isolated, or dramatically contracted. The most common founder mutations described thus far are the *BRCA1 185delAG* and *BRCA2 6174delT* mutations, which occur in about 1.0 and 1.4% of Ashkenazi Jews, respectively.[10,11] A third less common founder mutation (*BRCA1 5382insC*) also has been noted in Ashkenazi populations. These three mutations account for 98 to 99% of the *BRCA1/BRCA2* mutations identified in Ashkenazi Jews.[9] Today, most of the Ashkenazi Jews live in the United States, Israel, South America, South Africa, Australia, and New Zealand. One Israeli study, with 199 Ashkenazi women and 44 non-Ashkenazi women, found that about half of women with ovarian cancer and one-third of women with breast cancer had one of the three Ashkenazi founder mutations.[12] Certain founder mutations have also been identified in populations from the Netherlands, Sweden, Hungary, Iceland, and French Canada.

Male breast cancer cases are likely to harbor an inherited *BRCA2* mutation and should be specifically included in the assembled pedigree.[12–14] The ratio of female-to-male births in an affected family may also provide important information about a hereditary cancer syndrome.[12,13,15] *BRCA1* and *BRCA2* mutations appear to statistically decrease the number of male offspring in mutation carriers, while not affecting overall fertility.[16]

Once a family is suspected of having a hereditary cancer syndrome, genetic counselors should be involved in all phases of the genetic risk assessment and testing process.[3] A list of trained counselors and their contact information in the Unites States is available on the National Cancer institute (NCI) website at http://www.cancer.gov/cancertopics/genetics/directory. Extensive nondirective counseling and education is essential prior to genetic testing. Individuals should understand the risk of testing positive, potential benefits of the test, and the social and psychological implications of testing (see Table 21.2 NOW 2 for a summary of the benefits and limitations of genetic testing). The American Society of Clinical Oncology has outlined the basic elements of informed consent for genetic testing for cancer susceptibility, which should be met prior to ordering a test.[17] For these reasons, direct-to-consumer genetic testing has been discouraged by leading professional societies and bioethicists.[17–20] If direct-to-consumer testing is performed, the companies involved have an obligation to ensure that appropriate counseling occurs.

Several algorithms have been developed for risk assessment of the likelihood of carrying a *BRCA1* or *BRCA2* mutation, including BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system.[21] Of these, the BOADICEA algorithm appears to be the most accurate.[21] After pedigree analysis and risk assessment,

TABLE 21.2 Benefits and Limitations of Genetic Testing

Possible Benefits and Limitations Associated With Genetic Testing[a]

The potential benefits of testing include the following:

- Reassurance and reduced uncertainty.
- Facilitation of informed decision making about cancer prevention, including risk-reducing surgery and therapy for an existing breast cancer.
- Testing may satisfy a desire to obtain information for other family members, particularly one's children.
- Test results may help guide reproductive plans or choices.

Limitations and/or risks of testing include the following:

- A positive test result for a known susceptibility mutation indicates that the individual has an increased risk of developing cancer; however, it is not inevitable that a cancer will develop.
- Uninformative result or a "variant of uncertain significance."
- The psychosocial impact may be considerable. A common reason for declining genetic testing is the fear of breach of privacy and genetic discrimination in the areas of health and life insurance or employment.

[a]A positive results means that a deleterious mutation was identified. A true negative result occurs when an individual tests negative for a mutation that has already been identified in his or her family. An uninformative result occurs when no deleterious mutations are found in a high-risk individual who is the first to be tested in a family. This may occur when a deleterious mutation or rearrangement is present but cannot be detected by available methods; another, a rare gene or one that has not been isolated yet is involved; or the individual being tested developed sporadic rather than hereditary cancer. A "variant of uncertain significance" is an uninformative result as the significance of the variant is not well established; in these cases, further testing of family members may be helpful.

women who have a 20 to 25% risk of harboring a genetic mutation should be offered genetic testing.[3] This group includes women with a personal history of both breast and ovarian cancer, women with ovarian cancer and a family history of premenopausal breast cancer, women in Ashkenazi families with early onset breast cancers, women with male breast cancer in relatives, and women in known *BRCA* families.[3]

A second group of women with an inherited risk of 5 to 10% can be considered for genetic testing. This group includes women with premenopausal breast cancer; women who have personal histories of gynecologic malignancies, including ovarian, fallopian tube, or peritoneum; bilateral breast cancer survivors; Ashkenazi Jewish women with familial breast cancers in the 40s and 50s; women breast cancer survivors younger than age 50 years with other family history of breast cancer at age younger than 50 years, or multiple cases of breast cancer.[3] A list of testing laboratories is available through the Gene Tests website at www.genetests.org.

The use of predictive models to ascertain the likelihood of finding a *BRCA* mutation can be cumbersome for clinicians. As a result, consensus guidelines with criteria for genetic testing have been developed by several groups, including the American College of Obstetricians Gynecologists (ACOG) and the National Comprehensive Cancer Network (NCCN) (see Tables 21.3 and 21.4).

Testing should be offered to both women and men in a high-risk family.[22,23] In the United States, most insurance companies will cover the majority of the costs of commercial *BRCA* testing in appropriate candidates, although a letter of medical necessity stating the potential impact of a positive test result on surveillance or possible surgical options may be needed. Most individuals who seek genetic counseling elect to undergo cancer genetic testing. If possible, a family member who has already had cancer should be tested first. If a mutation is found in an affected individual, this greatly facilitates testing of other family members for this specific mutation. Test results should be conveyed in a setting that includes multidisciplinary input from genetic counselors and clinicians. Additional psychological support and encouragement is offered at this juncture because both positive and negative test results can cause significant distress.[24] The lifetime cancer risk for mutation carriers, as well as the options for prevention, should be reviewed. Patient disclosure of their genetic testing results to other potentially affected family members should be discussed and encouraged, but the decision to disclose those results remains with the patient.[22] Some families with a strong cancer history do not carry a mutation in a known susceptibility gene. Referral of these families to institutions with expertise in cancer genetics will assist in the identification of other cancer-causing genes through more intensive genetic analysis and ongoing research projects. In the meantime, clinical decisions in such families are made on a case-by-case

TABLE 21.3 Criteria for Genetic Risk Assessment

Patients with greater than an approximate 20–25% chance of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment is recommended:

- Women with a personal history of both breast cancer and ovarian cancer[a]
- Women with ovarian cancer[a] and a close relative[b] with ovarian cancer or premenopausal breast cancer or both
- Women with ovarian cancer[a] who are of Ashkenazi Jewish ancestry
- Women with breast cancer at age 50 years or younger and a close relative[b] with ovarian cancer[a] or male breast cancer at any age
- Women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger
- Women with a close relative[b] with a known *BRCA1* or *BRCA2* mutation

Patients with greater than an approximate 5–10% chance of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment may be helpful:

- Women with breast cancer at age 40 years or younger
- Women with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high grade, serous histology at any age
- Women with bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age 50 years or younger)
- Women with breast cancer at age 50 years or younger and a close relative[b] with breast cancer at age 50 years or younger
- Women of Ashkenazi Jewish ancestry with breast cancer at age 50 years or younger
- Women with breast cancer at any age and two or more close relatives[b] with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed at age 50 years or younger)
- Unaffected women with a close relative[b] that meets one of the previous criteria

[a]Cancer of the peritoneum and fallopian tubes should be considered a part of the spectrum of the hereditary breast and ovarian cancer syndrome.
[b]Close relative is defined as a first-degree relative (mother, sister, daughter) or second-degree relative (grandmother, granddaughter, aunt, niece).
From American College of Obstetrician and Gynecologists. ACOG Practice Bulletin No. 103: hereditary breast and ovarian cancer syndrome. *Obstet Gynecol.* 2009;113:957–966.

TABLE 21.4 National Comprehensive Cancer Network Criteria for Breast Cancer Genetics Referral

Criteria for Further Genetic Risk Evaluation[a]

An affected individual with one or more of the following:

- A known mutation in a breast cancer susceptibility gene within the family
- Early-age-onset breast cancer[b]
- Triple negative (ER−, PR−, HER2−) breast cancer
- Two breast cancer primaries[c] in a single individual
- Breast cancer at any age, and:
  - ≥1 close blood relative[d] with breast cancer ≤50 y, or
  - ≥1 close blood relative[d] with epithelial ovarian[e] cancer at any age, or
  - ≥2 close blood relatives[d] with breast cancer and/or pancreatic cancer at any age
  - From a population at increased risk[f]
- ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract[g]; diffuse gastric cancer[h]
- Ovarian[e] cancer
- Male breast cancer

An unaffected individual with a family history of one or more of the following[f]:

- A known mutation in a breast cancer susceptibility gene within the family
- ≥2 breast primaries in single individual
- ≥2 individuals with breast primaries on the same side of family (maternal or paternal)
- ≥1 ovarian[e] cancer primary from the same side of family (maternal or paternal)
- First- or second-degree relative with breast cancer ≤45 y
- ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract[g]; diffuse gastric cancer[h]
- Male breast cancer

[a]The criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

[b]Clinically use age ≤50 y because studies define early onset as either ≤40 or ≤50 y.

[c]Two breast primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

[d]Close blood relatives include first-, second-, and third-degree relatives.

[e]For the purposes of these guidelines, fallopian tube and primary peritoneal cancers are included. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome/hereditary non-polyposis colorectal cancer; be attentive or clinical evidence of this syndrome.

[f]For populations at increased risk, requirements for inclusion may be modified (e.g., women of Ashkenazi Jewish descent with breast or ovarian or pancreatic cancer at any age).

[g]For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, STK11 testing should be considered.

[h]For lobular breast cancer with a family history of diffuse gastric cancer, *CDH1* gene testing should be considered.

basis. In some cases, preventive strategies, including surgical prophylaxis, may be warranted even when genetic testing does not reveal an alteration in a known cancer susceptibility gene.

In studies of high-risk hereditary breast and ovarian cancer clinics, between 60 to 64% of women opt to be tested for genetic mutations.[25,26] The most common reasons for declining testing include lack of health insurance, fear of insurance discrimination based on test results or simply having testing done, concerns about the accuracy of the tests, and the possible emotional impact of test results on the patient and her family.[27]

HEREDITARY OVARIAN AND BREAST CANCER GENETICS

Autosomal dominant hereditary syndromes account for about 5% of breast cancers and 10% of ovarian cancers. Women with hereditary breast and ovarian cancer syndrome have a lifetime risk of breast cancer of 50 to 85%.[28,29] This wide range in reported risk is likely because of variations in risk due to penetrance and risk modifiers among the different study populations. Germline mutations in *BRCA1* and *BRCA2* account for the vast majority of high-penetrance hereditary ovarian cancers and at least half of hereditary breast cancers. These mutations may also be associated with increased risk for other malignancies (see Table 21.5). Population-based studies have demonstrated that *BRCA* mutations are rare in the non-Ashkenazi general population, affecting approximately 1 in 800 to 1 in 1000 individuals.[30,31] In the Ashkenazi Jewish population, the *BRCA1/2* founder mutation carrier rate is estimated at 2.5%, affecting 1 in 40 Ashkenazi Jews.[32,33] A variant in the *CHEK2* gene (1100del C) has been identified that is present in about 1% of the population and this variant increases risk of breast cancer by about two-fold.[34]

Mutation carriers of the *BRCA1* and *BRCA2* genes have only one functional allele of these genes in their cells, not two. This results in an increase in genomic instability and tumorigenesis. It is not clear why these mutations predispose mainly to breast and ovarian cancer. There are over a thousand known mutations in *BRCA1* and *BRCA2* genes and most of these lead to a truncated protein when they are translated while others may result in an abnormal amount or conformation of the *BRCA1* and *BRCA2* protein(s).

Patients with *BRCA1* or *BRCA2* mutations who develop breast cancer have an increased risk of second breast cancers. The rates of contralateral breast recurrence in patients with *BRCA*-associated breast cancer at 5 and 10 years are 11 to 20% and 25 to 27%, respectively.[35,36] The risk appears to be related to the patient's age at the first diagnosis of breast cancer. Although not as well defined, there is an increased risk for ipsilateral breast cancer recurrence over time, with most of these representing second primary cancers rather than local recurrences.[37]

BRCA1

The *BRCA1* gene is a very large gene of 7.8 kb, encoding a protein of 1863 amino acids, located on chromosome 17q21.[38] *BRCA1* plays roles in repair of double-stranded

TABLE 21.5 Estimated Cancer Risks Associated With *BRCA1* and *BRCA2* Mutations

Cancer Type	Risk in *BRCA1/2* Carriers to Age 70 Years	General Population Risk to Age 70 Years	Comments
Breast	40 to 75%	7%	The range of risk reported in the literature is wide. In most studies, risk in *BRCA1* carriers is higher than that observed in *BRCA2* carriers. The incidence of breast cancer diagnosed younger than 50 years of age is higher in *BRCA1* carriers compared to *BRCA2* carriers, but both groups have an increased risk of premenopausal breast cancer, as well as increased lifetime risks.
Contralateral (opposite) breast	*BRCA1*: up to 65% *BRCA2*: up to 50%	0.5 to 1% per year after diagnosis	Risk is affected by other factors such as tamoxifen use and oophorectomy (ovary removal). For *BRCA1/2* carriers who have had lumpectomy: Risk of developing a second breast cancer in the affected breast appears to be elevated over long follow-up periods.
Ovarian	*BRCA1*: Approximately 40% *BRCA2*: Approximately 15%	<1%	The risk estimates provided here are representative of findings from multiple studies. The incidence of ovarian cancer diagnosed younger than 50 years of age is higher in *BRCA1* carriers, and overall rare in all carriers younger than 40 years old; risk of fallopian tube cancer is also substantially elevated.
Colon	Unclear	2%	If elevated, risk is small; studies have not been consistent about whether risk is elevated.
Prostate	Elevated; absolute risk not well defined	8% Whites 12% African Americans	Risk appears to be higher in *BRCA2* carriers and possibly in men younger than 65 years old.
Male breast	Elevated but <10%	<1%	Risk appears to be higher in *BRCA2* carriers; rarely occurs in men younger than age 50.
Pancreatic	Elevated but <10%	<1%	Risk appears to be higher in *BRCA2* carriers.
Other bites	To be determined	Varied	These sites may include cancer of the stomach and skin (melanoma).

These risks are estimates based on review of the literature. Specific studies have reported risks that are lower or higher than the ranges or estimates quoted; however, the estimates reported here are representative of findings from high-quality studies. Risks will also vary based on an individual's current age and other risk factors.
Reproduced with permission from Carlson KJ. Screening for ovarian cancer. UpToDate Web site. http://www.uptodate.com/contents/screening-for-ovarian-cancer. Accessed November 26, 2013.

DNA breaks, regulation of gene transcription and association with other cell signaling molecules not involved in DNA repair. Loss of *BRCA1* function initiates the development of other genetic alterations through the inability to repair double-stranded DNA damage that eventually leads to clinically recognizable cancer.[39]

The lifetime risk of breast cancer by age 70 years in *BRCA1* mutation carriers is about 65 to 75%.[40] The lifetime risk (by age 70 years) of ovarian cancer in *BRCA1* carriers is now believed to be as high as 39 to 46%, which is higher than for *BRCA2* mutation carriers.[40] In addition, some studies have suggested that *BRCA1* mutation carriers have a higher risk of prostate, colon, pancreatic, and stomach cancers.[13,41] A more recent study of Ashkenazi Jewish carriers confirmed the increased risk of prostate cancer, but colon cancer risk was not increased.[13,32] Pancreatic cancer risk is elevated in *BRCA1* as well as *BRCA2* carriers.[42] Increased breast cancer risk begins earlier than risk for ovarian cancer.[41] Carriers have an increased breast cancer risk in their twenties, whereas their ovarian cancer risk does not rise appreciably until the mid-thirties. In addition to risk of an initial breast cancer, *BRCA1* mutation carriers are at about a 40% risk of developing a second primary breast cancer by the age of 70 years.[13]

Various *BRCA1* mutations may differ in the extent to which they predispose to breast or ovarian cancer. As a result, individuals in the same family may carry the same mutation but have significantly different types of cancer and even ages of onset. Mutations in the carboxy terminus of the gene may result in a higher frequency of breast cancer relative to ovarian cancer.[43–45] Conversely, ovarian cancer is associated in some studies with mutations in the middle of the gene, the area called the ovarian cancer cluster region, between bases 2401 and 4190.[46] However, these findings are not consistent enough to guide clinical management or recommendations.

Differences in penetrance have also been noted among families with identical *BRCA1* mutations. Two hypotheses, both of which may be relevant, have been proposed to explain variable penetrance. First, other gene variants, including single nucleotide polymorphisms (SNPs), may modify the penetrance of *BRCA1*, that is, gene–gene interactions may contribute to differences in cancer expression. Alternatively, it is possible that gene–environment interactions may modify risk. For example, pregnancy and oral contraceptive pill use decrease the risk of ovarian cancer in the general population. Reproductive risk factors that affect breast and

ovarian cancer incidence in the general population may also modify risk in *BRCA1* carriers. In some studies, oral contraceptives were found to reduce ovarian cancer risk by 50% in women with hereditary ovarian cancer syndromes.[47] These two hypotheses are not mutually exclusive, because *BRCA1* itself has been found to modify estrogen receptor α.[48]

BRCA1-associated breast cancers cluster in the basal-like gene expression pattern.[49] *BRCA1*-associated breast tumors are typically estrogen and progesterone receptor negative, as are basal cancers. Amplification of HER2/neu is uncommon in *BRCA1*-associated tumors. *BRCA1*-associated breast cancers have other high-risk features, including high-grade, high proliferative rate, no special type (NST) ductal carcinoma histology, and medullary histology.[50] They also have lymphocyte and plasma cell infiltrates. Despite these poor prognostic features, *BRCA1*-associated breast cancers presented at lower stage and have a relatively favorable outcome.[51] The addition of chemotherapy to conservative surgery for breast cancer increased the survival of Ashkenazi women with *BRCA* mutations in one study.[52]

The histologic features of ovarian cancers in *BRCA1* carriers do not differ strikingly from sporadic cancers. Most cases are advanced stage, moderate to poorly differentiated serous cancers. *BRCA1*-associated high-grade serous ovarian cancers are histologically indistinguishable from fallopian tube or primary peritoneal cancers, which also are more common in *BRCA1* carriers.[13,53–56] The finding that the spectrum of *BRCA1*-associated serous cancers includes the tubal epithelium has led some to hypothesize that the fallopian tube is the primary site of origin of ovarian and primary peritoneal serous carcinomas.[57,58] This theory is further supported by the finding of intraepithelial carcinomas in the tubal fimbria of some prophylactic surgery specimens from mutation carriers.[59–62] In some cases, tubal in situ carcinomas (TICs) have been found adjacent to invasive disease, which provides further evidence that they are precursor lesions. TICs have been shown to overexpress mutant *p53*, as do most high-grade serous cancers.[63,64]

Survival of *BRCA1* carriers with ovarian cancer is longer than sporadic cases matched for age, stage, and other prognostic factors.[65–69] This is thought to be due to a better response to platinum-based chemotherapy because of loss of *BRCA1*-associated repair of double-stranded DNA repair.[69,70] It also has recently been shown that agents that inhibit the enzyme polyADP-ribose polymerase (PARP), which is involved in single-stranded DNA repair, are highly active in *BRCA1*-associated cancers, but not in sporadic cases.[71–74] Abrogation of both single- and double-stranded DNA repair in these cancers makes them acutely sensitive to DNA damaging chemotherapy agents. Acquisition of platinum resistance in *BRCA* mutant tumors may be associated with secondary genetic changes in *BRCA1* that restored full-length protein expression and function.[75]

BRCA2

A significant fraction of breast cancer families in which a *BRCA1* mutation was excluded were found to be linked to chromosome 13q12 in 1994.[76] *BRCA2* binds and regulates the strand invasion recombinase, which is necessary for proper recombination of double-strand DNA breaks. In 1995, this second breast cancer susceptibility gene (*BRCA2*) was identified.[77] Notable attributes of *BRCA2* families include early age of onset, most often in the last 40s or 50s, and the occurrence of male breast cancer.[78,79] Ovarian cancer is a less prominent feature of these families, and there are about 10 female breast cancer cases and 1 male breast cancer case for each ovarian cancer case in *BRCA2* families. Fallopian tube cancer risk is also increased.[53,54,56]

BRCA2 is responsible for a similar proportion of hereditary breast cancer as *BRCA1* (4 to 5%), and studies indicate that mutations in *BRCA2* confer a similar lifetime risk of female breast cancer as for *BRCA1*. The current estimated lifetime risk of ovarian cancer in *BRCA2* carriers is between 10 and 20%.[32,54,80,81] Ovarian cancer is most often observed in families with mutations in the large exon 11 in the Ovarian Cancer Cluster Region (OCCR).[9,82] Similar to *BRCA1*, the *BRCA2* gene appears to play a role in double-stranded DNA repair.[83] *BRCA2* is now known to be identical with a gene that causes some cases of Fanconi anemia.[84]

The clinicopathologic characteristics of *BRCA2*-associated breast cancers are similar to sporadic cases, but *BRCA2*-associated cases are less often tubular and are of higher grade.[85] *BRCA2*-associated cancers generally are of the luminal subtype and are often estrogen and progesterone receptor positive.[49] *BRCA2*-associated ovarian cancers are usually high-grade serous lesions, although some may be endometrioid. The risk of clear cell and mucinous cancers and borderline tumors is not increased in *BRCA1/2* carriers. Carriers of the *BRCA2* mutations are also at increased risk of other cancers, including prostate, laryngeal, and pancreatic cancer. Despite multiple cancer risks, women with *BRCA2* mutations have an increased life expectancy compared to *BRCA1* carriers, due to the increased rate and mortality from ovarian cancer in *BRCA1* carriers.[86]

Genetic Testing for Hereditary Ovarian and Breast Cancer

Mutations have been observed throughout the large *BRCA1* and *BRCA2* genes, and approximately 80 to 90% of the mutations predict truncated protein products.[87–90] Missense mutations alter a single amino acid in a full-length protein product and occur in about 10 to 15% of hereditary cases.[88,89] Alteration of a single amino acid may create a disease-causing mutation or may not affect gene function.[38] In some cases, biochemical

and computational analyses[73,90–93] of variants of uncertain significance have helped to clarify whether they represent clinically significant deleterious changes.[94–99] Segregation of a missense mutation with breast and ovarian cancer in a family suggests, but does not prove, its clinical significance.

Because mutations in *BRCA1* and *BRCA2* occur throughout these large genes, the most reliable method of detecting mutations is to sequence the entire coding region, including intronic splice sites. The sensitivity of DNA sequencing for detecting mutations is excellent and the false-negative rate is estimated to be very low. Although automated DNA sequencing is labor intensive and expensive, it remains the gold standard for mutational testing. However, some deleterious *BRCA1/2* mutations involve complex rearrangements of the gene that do not result in a sequence change, yet a functional protein product is not produced. Testing for these rare rearrangements with *BRCA1/2* Analysis Rearrangement Test (BART) analysis is appropriate in families with a very high predicted likelihood of carrying a *BRCA1/2* mutation in which no mutation is found in the coding sequence.[100,101]

Although mutations in *BRCA1* and *BRCA2* have been noted in some women in the absence of a family history of breast or ovarian cancer, the incidence is low and cost considerations prohibit *BRCA* mutational screening in the general population of the United States. *BRCA1/2* testing costs about $3,000. A postmenopausal woman with breast or ovarian cancer who does not have a family history of ovarian or breast cancer has a 3% risk of carrying a mutation. At the other extreme, in families with two cases of breast cancer and two cases of ovarian cancer, the probability of finding a mutation may be as high as 80 to 90%.[45] Most experts believe it is reasonable to offer testing when the family history suggests at least a 5 to 10% probability of finding a mutation.[3] In practical terms, this translates into two first-degree relatives with either ovarian cancer at any age, breast cancer prior to age 50 years, and those in a high-risk ethnic group such as Ashkenazi Jews. In some families with a paucity of females, it may be reasonable to recommend testing in families with fewer cancer cases.[102]

Within the Ashkenazi Jewish population, 1 in 40 individuals carry one of three germline *BRCA1* or *BRCA2* mutations.[30,80,81,103,104] Testing for these three founder mutations is much less expensive than full sequencing, and some believe this should be offered to all Ashkenazi women with breast and/or ovarian cancers.[102,105,106] It also has been suggested that perhaps all women with high-grade serous ovarian cancers, particularly those who have a family history of breast and ovarian cancer, should undergo full *BRCA1/2* testing. The mutation rate may be as high as 20% in this subgroup, and those found to be mutation carriers can be predicted to have a better prognosis and to respond well to platinum drugs and PARP inhibitors.[5,72,74] As the cost of DNA sequencing continues to fall in the future, this may facilitate more widespread genetic testing in women with ovarian cancer.

It is preferable to test affected individuals in a "high-risk" family first because a negative test in an unaffected individual may reflect failure to inherit the mutant allele, even though others in the family carry a mutation. If affected family members are deceased, tissue blocks may be retrieved from which DNA can be extracted and analyzed for a mutation. Once a specific mutation is identified in an affected individual, other family members can be tested at less expense because the analysis is focused on one specific mutation. Children of a parent with a *BRCA1* or *BRCA2* mutation have a 50% risk of inheriting the mutation.

Confidentiality remains a critical issue in cancer susceptibility testing. Misuse of genetic information potentially could have devastating consequences, including difficulty in securing employment and life, health, or disability insurance. Most individuals ask their insurance company to pay for *BRCA1/2* testing and are willing to have this information recorded in their medical records. With the 2008 passage of the federal Genetic Information Nondiscrimination Act (GINA; Pub L No. 110-233, 122 Stat 881), genetic information has acquired new safeguards.[107] In view of this, results of pedigree analysis and genetic testing can be entered into the medical record without fear that this will lead to liability with respect to health or life insurance or employment discrimination.

Clinical Management of *BRCA1* and *BRCA2* Mutation Carriers

With the discovery of *BRCA1* and *BRCA2*, only a minority of cases of familial ovarian cancer should have to be managed as in the past by simply recommending prophylactic bilateral salpingo-oophorectomy (BSO) on the basis of a strong family history.[108–110] Although the penetrance of various mutations is still somewhat uncertain, it is clear that carriers have a strikingly increased risk of ovarian/fallopian tube cancer relative to the general population.[44,82,111]

Risk-reducing options available to *BRCA1/2* carriers include prophylactic mastectomy, prophylactic BSO, chemoprevention, and increased surveillance. In women who have completed childbearing, the decision to pursue risk-reducing BSO is based on the strong protective effect of surgery and the high mortality rate of ovarian cancer.[112] Parous women older than 40 years of age with a personal history of breast cancer are also likely to choose prophylactic BSO over surveillance.[113] Internationally, the rates of acceptance of risk-reducing measures vary considerably.[114] Prophylactic BSO was the most commonly accepted measure (34.9 to 71%), whereas prophylactic mastectomy was much less commonly chosen (4.2 to 36.3%). Breast cancer

TABLE 21.6 Management Options for *BRCA1/BRCA2* Carriers

Ovaries

- Oral contraceptive pill until childbearing complete
- Risk-reducing salpingo-oophorectomy after childbearing complete, ideally between ages 35 and 40 years
- Biannual transvaginal ultrasound, CA-125 level, and physical/pelvic examination in women choosing not to have risk-reducing surgery or in untested high-risk women, starting at age 35 years or 5–10 years before the earliest ovarian cancer case in the family, whichever comes first (preferably day 1–10 of the menstrual cycle if premenopausal)

Breasts

- Annual mammogram and breast MRI starting at age 25 years or earlier, depending on the earliest age of onset in the family
- Monthly self breast exam starting at age 18 years
- Clinical breast exams, two to four times annually, starting at age 25 years
- Chemoprophylaxis in individuals declining mastectomy
- Risk-reducing bilateral total mastectomy
- Risk-reducing bilateral salpingo-oophorectomy after Ge 35 or once childbearing is complete

chemoprevention with the antiestrogens tamoxifen or raloxifene was not generally pursued (0 to 12.4%).

Patients who desire continued fertility may be offered surveillance options such as bi-annual screening with CA 125 and ultrasound, starting at age 35 years or 5 to 10 years before the earliest ovarian cancer case in the family, whichever comes first[115] (see Table 21.6 for management options for *BRCA1/BRCA2* carriers). Such an approach is reasonable but lacks proven efficacy in reducing cancer mortality because even with intensive screening, ovarian cancers are usually diagnosed at an advanced stage.[116–119] Trials of ovarian cancer screening in mutation carriers are ongoing in both the United States and United Kingdom, but final results have not yet been published. Carriers of a *BRCA* mutation have similar fertility rates to noncarriers in most studies.[16,120] However, occult primary ovarian insufficiency has been associated with *BRCA* mutations in patients undergoing assisted reproduction.[121]

Another ovarian/fallopian tube cancer risk-reducing strategy for *BRCA* mutation carriers may be the use of oral contraceptives, which decrease the risk of ovarian cancer in the general population by as much as 80%. Oral contraceptives are a particularly attractive alternative for young women who have not yet completed childbearing, and some data indicate that *BRCA* mutation carriers may benefit from oral contraceptive use.[47,122–125] Some studies have attributed an increased risk of breast cancer in *BRCA* carriers to use of oral contraceptives,[126,127] especially when oral contraceptive pills (OCPs) were started less than 20 years of age.[128] However, other groups have not validated this association.[129,130] Data thus far are for oral contraceptives, as other formulations have not been studied for use in ovarian cancer risk reduction among women with *BRCA1* or *BRCA2* mutations. It seems reasonable to think they would have a similar effect.

Risk-Reducing Bilateral Salpingo-Oophorectomy

Fortunately, the incidence of ovarian cancer in *BRCA* carriers does not begin to rise appreciably until the mid- to late 30s when most women have completed their family.[41] Risk reducing BSO (rrBSO) after completion of childbearing represents a rational approach to decreasing ovarian cancer mortality in mutation carriers. The term "risk-reducing BSO" is now preferred to "prophylactic BSO," as there is still a residual risk of primary peritoneal cancer. Surveys show that 74 to 75% of high-risk women undergoing *BRCA* testing would consider rrBSO.[112,131] rrBSO is considered to be the most effective intervention in *BRCA1* carriers and increases survival by 15%.[132]

rrBSO is an attractive clinical option in *BRCA* mutation carriers for several reasons (see Table 21.7 for pros and cons of rrBSO). First, this procedure can be performed in an outpatient setting using minimally invasive surgery, and the costs will generally be covered by medical insurance.[133] BSO causes only modest changes in body image and self-esteem and is not viewed as cosmetically mutilating by most women. In addition, there is now strong evidence that BSO provides strong protection against ovarian and tubal cancers as well as breast cancer. In one large study, the risk of breast and ovarian cancer was decreased 75%.[134] Another large multicenter study followed women for a mean of 8.8 years after BSO and concluded that the procedure reduced the risk of epithelial ovarian cancer by 96%.[135] BSO reduced the risk of ovarian, primary peritoneal, and fallopian tube cancers by 98% in another study of 248 cases and 245 controls, all of whom were *BRCA* mutation carriers.[136]

There is a 4 to 8% risk of detecting occult ovarian malignancy at the time of rrBSO or in the final pathology report.[137,138] This risk is higher (20%) in women undergoing rrBSO at or more than 45 years of age. A

TABLE 21.7 Pros and Cons of Risk-Reducing Salpingo-Oophorectomy

Pros

Decreases ovarian and fallopian tube cancer incidence and mortality
Can be delayed to allow completion of childbearing
Minimally invasive approach possible in most cases
Impact on body image generally acceptable
Estrogen replacement can ameliorate consequences of surgical menopause
Decreases breast cancer risk

Cons

Cost
Potential surgical morbidity and mortality
Small but residual potential for subsequent primary peritoneal carcinoma
Surgical menopause in premenopausal patients who do not receive hormone replacement

From Karlan B, Berchuck A, Mutch D. The role of genetic testing for cancer susceptibility in gynecologic practice. *Obstet Gynecol.* 2007;110(1):155–167.

hysterectomy may be performed along with BSO when there are other gynecologic indications or if the woman has Lynch syndrome, is planning to take tamoxifen, or if she wishes to take unopposed estrogen therapy after rrBSO.[139] The data regarding an increased risk of endometrial adenocarcinoma in women with *BRCA* mutations are not conclusive, although if there is an increase, it appears small.[140]

Several areas require particular attention when performing BSO in *BRCA* carriers. In women with *BRCA* gene mutations, some ovarian cancers are initiated in the fallopian tubes, so all ovarian and fallopian tube tissue must be removed. Complete cornual resection does not appear to be necessary, however, because there have been no reports of malignant transformation in the intramural tubal remnant.[141] In cases where scar tissue or endometriosis has encapsulated the adnexa, careful but complete dissection must be done to ensure full removal of the ovaries and tubes. Dense adhesions may require a conversion to a laparotomy to ensure complete removal of both tubes and ovaries.

It is critical that the surgical pathologist be notified that a BSO specimen is from a *BRCA* mutation carrier. The specimen should be serially multistep sectioned at 2 to 3 mm intervals through *both* the ovaries and the fallopian tubes and examined microscopically for occult carcinoma.[142] In one series, occult cancers were found in 12% of cases,[143,144] although the rate is currently thought to be 2.5%.[145] The pathologist should look carefully for the presence of premalignant lesions in the fallopian tubes as well as early invasive cancers in the tubes and ovaries.[146,147] Tubal intraepithelial carcinoma (TIC), has been identified in as a putative precursor for pelvic serous malignancies.[57] In addition, pathologists may consider staining TIC lesions to detect overexpression of mutant p53 protein, which is often found in these lesions.[57]

Malignant cells have also been found in pelvic washings performed at the time of rrBSO.[148] In one study, pelvic washings were positive for malignant cells in women with occult fallopian tube cancers.[149] In view of this, pelvic washings should always be performed and the surgeon should carefully inspect the peritoneal surfaces, particularly in the pelvis. This may be aided by the magnification provided by minimally invasive surgery. Any areas suspicious for cancer should be biopsied. The surgeon and the patient should be prepared in advance for the discovery of invasive cancer and the need for additional staging and/or debulking surgery.

Because many serous cancers in *BRCA* carriers appear to arise in the fallopian tubes, it is important to remove the tubes completely.[13,53,56,117] However, the distal fimbrial end of the tube is thought to be the main area at risk. A concomitant hysterectomy ensures resection of the cornual portion of the tube but may not be desired by the patient.[149] The possibility of an increased risk of uterine cancer in *BRCA1/2* carriers remains controversial[5] and generally does not dictate removal of the uterus. The decision to undergo hysterectomy with rrBSO remains an individual decision based on weighing the additional surgical risks of bleeding and infection against existing gynecologic indications for hysterectomy, and the advantage of simplification of posthysterectomy hormone replacement therapy and/or chemoprophylaxis.[3] Women who retain the uterus will require a progestin along with estrogen to protect against endometrial cancer. Those who receive tamoxifen in the context of breast cancer treatment or prevention have a two- to three-fold increased risk of uterine cancer, but tamoxifen use in this context has decreased in favor of more selective estrogen receptor modulators and aromatase inhibitors.

Treatment and Surveillance After Risk-Reducing Bilateral Salpingo-Oophorectomy

In premenopausal women without a personal history of breast cancer, the risk and benefits of estrogen replacement should be discussed as a means of avoiding the deleterious effects of premature menopause.[150] It has long been known that reduced estrogen exposure due to surgical or natural premature menopause reduces breast cancer risk, and oophorectomy also reduces risk in *BRCA* carriers.[134,151,152] rrBSO decreases the risk of breast cancer in *BRCA1/2* carriers by 51 to 60%.[153–155] Subsequent hormone replacement therapy does not appear to alter the subsequent risk of breast cancer after rrBSO, although data is limited.[155,156]

One concern regarding rrBSO is the observation that a small fraction of women subsequently have developed serous peritoneal carcinomatosis indistinguishable from ovarian cancer; the risk is estimated to be just under 2%.[152,157–159] This occurs infrequently, however, and some of these cases may reflect recurrence of occult ovarian or tubal cancers that were not detected at the time of BSO. There are no data on the impact of hormone therapy on the risk of ovarian or peritoneal cancer after rrBSO.

Hereditary Breast Cancer Surveillance and Treatment

Prevention of breast cancer mortality in *BRCA1* and *BRCA2* carriers presents different issues because these cancers are much more readily detected at an early stage than ovarian cancers. As a result, overall breast cancer 5-year survival in the United States is approximately 70% compared with only 30 to 40% for ovarian cancer. Furthermore, unlike BSO, mastectomy causes marked alterations in self-esteem and body image, even when breast reconstruction is performed. However, the effectiveness of mastectomy in reducing breast cancer risk

in *BRCA* mutation carriers is significant.[160] For *BRCA2* carriers, a prophylactic mastectomy is the single most effective intervention in terms of overall survival.[132] A bilateral mastectomy is recommended in *BRCA* carriers because both breasts harbor the same deleterious predisposing mutation.[161,162] Previous surgical practice for prophylactic mastectomies included subcutaneous mastectomies in which most of the breast tissue was removed, but the nipple was preserved. Advocates of prophylactic mastectomy today generally recommend total mastectomy, including the tissue under the nipple, because malignancy can potentially form in the nipple. Even if a total mastectomy is performed, there is no guarantee that all breast tissue will be successfully excised so while bilateral risk-reducing mastectomy decreases the incidence of breast cancer by as much as 90% among patients with *BRCA1* or *BRCA2* mutations, or those with a risk of hereditary breast cancer, it is not 100% effective in eliminating all risks.

Although some women will continue to choose mastectomy, close surveillance with mammography, magnetic resonance imaging (MRI) of the breast, self-breast exam, and clinical breast examination may prove equally effective in reducing mortality in view of the good prognosis for women with early breast cancer. In a large *BRCA1* kindred in Utah, 82% of female *BRCA1* mutation carriers obtained a mammogram in the year after their genetic diagnosis, but only 11% were considering a mastectomy.[23] Beginning in the 20s, biannual clinical breast exams are recommended for individuals choosing intensive screening.[163] New National Comprehensive Cancer Network (NCCN) surveillance recommendations for *BRCA* carriers include annual mammograms and annual breast MRI screening beginning at age 25 years.[115] The American Cancer Society recommends MRI screening for women who are *BRCA* carriers, relatives of *BRCA* carriers or whose calculated risk of breast cancer is less than 25%.[164]

Contrast-enhanced MRI has emerged as a cost-effective screening tool in young women in high-risk families because breast density does not affect the MRI imaging, as it does in mammography, which lowers the sensitivity of mammography in women with *BRCA* mutations.[165] The lower sensitivity of mammography alone may also be due to differences in morphologic features of breast cancers associated with *BRCA* mutations, and the fact that many of the histopathologic findings found in women undergoing prophylactic mastectomy because of a strong family history of breast cancer are not detectable on mammography.[166,167] Breast MRI is more sensitive but less specific than mammography for detecting invasive cancers in high-risk women.[168] The combined use of mammography and breast MRI is associated with higher sensitivity for the detection of breast cancer than MRI alone and the number of patients diagnosed at an earlier stage of disease is increased.[169,170] Screening should be initiated at least 5 years before the youngest case of breast cancer in the family.

BRCA1–associated breast cancers differ from those due to *BRCA2* mutations and other familial cases of breast cancer. They are more likely to be larger, be poorly differentiated, and have a higher histologic grade with a high proliferative rate. Breast tumors in *BRCA1* and *BRCA2* mutation carriers also differ in estrogen receptor status; *BRCA1* tumors are more likely to lack estrogen and progesterone receptors.[171]

There is not a lot of data addressing the breast cancer prevention impact of tamoxifen in patients with *BRCA1* or *BRCA2* mutations. In one study, tamoxifen, when started at age 35 years, reduced breast cancer incidence by 62% among healthy *BRCA2* carriers but not in *BRCA1* carriers, although the number of women in the study who were mutation carriers was small.[171] It is also not clear if there is any additive effect in instances where a woman with a *BRCA1* or *BRCA2* mutation has undergone bilateral oophorectomy. However, chemoprophylaxis with tamoxifen did not raise the risk of ovarian cancer in *BRCA* carriers who had not had BSO.[172] Tamoxifen does reduce the risk of contralateral breast cancer in patients with *BRCA1* or *BRCA2* mutations.[173] It is not known if tamoxifen reduces the risk of recurrence in *BRCA1* or *BRCA2* patients with hormone receptor–negative breast cancers.

Less Common Breast and/or Ovarian Cancer Susceptibility Genes

Although the most common cause of hereditary breast and ovarian cancer syndrome is germline mutations in *BRCA1* and *BRCA2*, there are other hereditary syndromes that increase susceptibility to breast and/or ovarian cancer. Women who have had negative *BRCA1/2* testing now have additional gene panel testing options which examine genes that interact with the DNA repair pathway containing *BRCA1/2*, including *RAD51C*,[173a] *RAD51D*,[173b] *PALB2*,[173c] and *BRIP1*.[173d] In addition to increased risk in these cancers, these syndromes are associated with an increased incidence of other cancers, and while the mutations are highly penetrant, the risk(s) for developing cancer as well as the manifestations of these genes in individuals are variable.

Li-Fraumeni syndrome is an autosomal dominant condition that is associated with the development of particular cancers in early childhood as well as an increased lifetime risk of developing multiple primary cancers, including sarcomas, breast, brain, and other cancers. The majority of Li-Fraumeni cases are caused by a tumor protein 53 gene (TP53) germline mutation. Patients with Li-Fraumeni have an absolute risk for developing any cancer of about 50% by the age of 30 years and up to 90% by the age of 60 years.[174] Breast cancer is one of the most frequent malignancies in Li-Fraumeni syndrome and is often diagnosed before the age of 45 years.[175] Genetic counseling and testing for *TP53* mutation should be considered in patients are from a family with known *TP53* mutation,

who satisfy the criteria for Li-Fraumeni syndrome, or who have early onset breast cancer (before the age of 30 years) without detectable *BRCA1* or *BRCA2* mutations. Breast cancer surveillance recommendations for these patients include clinical breast exams every 6 months and annual mammograms and/or breast MRI starting at ages 20 to 25 years or 5 to 10 years before the earliest known breast cancer in the family, whichever comes first.

Mutations in the checkpoint kinase 2 (*CHEK2*) gene are associated with a two- to three-fold increased risk in breast cancer and have been identified in approximately 5% of breast cancer patients from non–*BRCA* breast cancer families. *CHEK2* testing is not done routinely, however, because the cancer risks associated with *CHEK2* mutation and implications for clinical management for patients with these mutations is not well defined.[175]

Ataxia-telangiectasia is an autosomal recessive disorder that is characterized by progressive cerebellar degeneration (ataxia), dilated blood vessels in the eyes and skin (telangiectasia), immunodeficiency, chromosomal instability, increased sensitivity to ionizing radiation, and a predisposition to cancer, especially lymphoma and leukemia. The defective gene has been designated the ATM gene; normally, the gene is involved in the detection and surveillance of DNA damage. Homozygous carriers are at increased risk for breast cancer and ovarian cancer but there is some evidence that among heterozygote carriers, there is a moderate increase in the risk of breast cancer as well.[176,177]

Cowden syndrome (also known as multiple hamartoma syndrome) is an autosomal dominant condition characterized by the development of multiple hamartomatous lesions (benign tumors that result from the overgrowth of normal tissue) and early onset breast, uterine, and nonmedullary thyroid cancer.[178] Up to 75% of women with Cowden syndrome have benign breast conditions, for example, ductal hyperplasia, fibroadenomas, and intraductal papillomatosis. Breast cancer develops in 25 to 50% of women with Cowden syndrome with most occurring premenopausally. Cowden syndrome is caused by mutations in the tumor suppressor phosphatase and tensin homolog (PTEN) gene. The diagnosis of Cowden syndrome is based primarily on clinical criteria although there are various clinical presentations. There is a clinical scoring system to help determine who may necessitate genetic testing available.[179] Many of the patients who meet the clinical diagnostic criteria for Cowden syndrome have no family history of the disease.

Peutz-Jeghers syndrome is an autosomal dominant condition characterized by hamartomatous polyps in the gastrointestinal (GI) tract and mucocutaneous melanin deposits in the mucosa of the mouth, lips, fingers, and toes. The polyps are found throughout the GI tract and may lead to intussusceptions and bowel obstruction. Patients are at increased risk for several different types of cancer, including breast cancer. The overall cumulative risk of cancer in these patients is 93% by the age of 65 years.[180] The syndrome is caused by germline mutations in a serine threonine kinase (STK11) on chromosome 19p13.3. The cumulative absolute risk of breast cancer between 15 and 64 years of age is estimated to be 55%, comparable to that seen in *BRCA1* and *BRCA2* mutation carriers. Ovarian cancer is also increased, with an estimated risk of 20% among affected women.

Hereditary diffuse gastric cancer syndrome is associated with inherited cadherin-1 (CDH1) gene mutations and is associated with a lifetime risk of gastric cancer of over 80%. It is also associated with an increased risk in the development of lobular breast cancer, with the cumulative lifetime risk in some families of almost 60%.[181,182] Breast cancer screening in female carriers starting at age 35 years with annual mammography and breast MRI is recommended, as is early prophylactic gastrectomy.

Neurofibromatosis-1 (NF-1) is characterized by cutaneous neurofibromas and malignant peripheral nerve sheath tumors, as well as learning disabilities. In one recent study, women with NF-1 had a five-fold increase in the risk of developing breast cancer before 50 years of age, and a three- to four-fold increase overall in lifetime breast cancer risk.[183]

Mutations in a gene called partner and localizer of *BRCA2* (PALB2) are associated with an increased risk of pancreatic cancer and a two- to four-fold increased risk of breast cancer in women, that is, an approximate lifetime risk of 18 to 35%. The association between these mutations and other cancer risks, as well as surveillance and management recommendations, is not well defined.

HEREDITARY COLON CANCER

Colon cancer represents the third most common cause of cancer mortality in American women after breast and lung cancer.[184] Colon cancer develops in a stepwise progression from normal mucosa, to hyperplasia and polyp, and finally, to dysplasia, cancer in situ, and invasive cancer.[7] Because this disease has a well-defined clinically recognizable precancerous phase, colon cancer mortality can be decreased by screening programs.[185] The American College of Gastroenterology (ACG) updated their Guidelines for Colorectal Cancer Screening in 2008.[186] They divided colorectal cancer (CRC) screening tests into those for cancer prevention and those for cancer detection. The ACG preferred CRC prevention test for the general population is currently colonoscopy every 10 years beginning at age 50 years; alternatives include flexible sigmoidoscopy every 5 to 10 years or computed tomography (CT) colonography every 5 years. The ACG-preferred CRC cancer detection test is annual fecal immunochemical test (FIT), replacing the previous guaiac testing. Alternatives for CRC cancer detection include annual Hemoccult Sensa, or fecal DNA testing every 3 years.[186] Unfortunately, available screening tests are underused, and half of all patients with colon cancer die of their disease.

Most colon cancers are believed to arise due to sporadic mutations that accumulate over a lifetime, but some cases are the result of a hereditary predisposition. Approximately 71,000 women were diagnosed with a CRC in the United States in 2009.[184] Of those women, 15% will have a first-degree relative with colon cancer. Individuals who have a first-degree relative with colon cancer are twice as likely to develop colon cancer compared with the general population.[187] The risk is substantially greater if the relative was younger than 45 years of age at diagnosis.

Familial Adenomatous Polyposis

The familial adenomatous polyposis coli (APC or FAP) syndrome is inherited as an autosomal dominant trait with almost complete penetrance.[188,189] FAP affects 1 in 7000 persons, accounting for about 1% of all colon cancers. Virtually, all individuals who inherit this syndrome develop hundreds of polyps throughout the colon and invasive colon cancer at a young age.[189] Each polyp is believed to have the same chance of malignant transformation as a sporadic polyp. The sheer number of polyps in the inherited syndrome makes the combined risk for malignant transformation at multiple sites substantial. Patients with this syndrome may also develop gastric, periampullary, and duodenal precancerous polyps. Other extracolonic tumors may include thyroid cancer (follicular or papillary), or hepatoblastoma.[190]

In 1991, Bodmer et al.[191] localized the gene-causing familial polyposis to chromosome 5q21. Most mutations in the FAP gene are frameshift or nonsense changes that cause early termination of the protein product. The exact function of the FAP protein remains unclear but is believed to act as a tumor suppressor. The FAP protein may also be involved in signal transduction, cellular adhesion, and microtubule function.[192,193]

Unlike most tumor suppressor genes in which inactivation of both copies of the gene is necessary, mutation of only one copy of the FAP gene is required for polyp formation.[194] Progression from polyp to a fully invasive cancer is accompanied by alterations in other genes such as p53, DCC (deleted in colon cancer), and K-*ras*.[195] In addition to being responsible for familial polyposis syndrome, the FAP gene is frequently mutated in the course of sporadic colon cancer development.[193]

Hereditary Nonpolyposis Colorectal Cancer (Now Referred to as Lynch Syndrome)

The most common form of hereditary colon cancer is hereditary nonpolyposis colorectal cancer (HNPCC), now referred to as Lynch syndrome, accounts for about 5 to 10% of CRCs. Lynch syndrome is an autosomal dominant disorder with a high penetrance of cancer in mutation carriers (about 80%) and is caused by germline mutations in one of several DNA mismatch repair (MMR) genes: *MSH2*, *MLH1*, *PMS1*, *PMS2*, *MSH6*, *MLH3*.[196,197] Mutations in the *MSH2* and *MLH1* genes appear to account for the majority of Lynch syndrome families in which mutations can be identified, and for 3 to 5% of all CRCs.[198]

The function of the DNA repair genes is well known from studies in yeast and bacteria. Mutation in DNA repair genes leads to the accumulation of mutations, particularly in areas of the DNA that have repetitive sequences (e.g., CACACA). These repetitive sequences, called microsatellites, are dispersed throughout all chromosomes and are a frequent site of mutations in humans who inherit mutations in one of the DNA repair genes. Although some microsatellites are within the coding sequence of genes, most reside in the intervening noncoding regions. Microsatellite mutations within growth regulatory genes may contribute to malignant transformation, but it is unclear whether microsatellite instability (MSI) outside genes is important in carcinogenesis or merely a symptom of the underlying problem.

Clinically, the colon cancers in Lynch syndrome occur at an earlier age than sporadic colon cancer (mean age of 48 years) and predominantly involve the right colon (70%), and there is a high rate of metachronous cancers.[199] Patients with Lynch syndrome generally form premalignant widely based sessile colonic adenomas rather than polyps. The adenoma-carcinoma sequence is believed to progress more quickly in Lynch syndrome and new cancers have occurred within 2 to 3 years of a negative colonoscopy. Colonic cancers in individuals with Lynch syndrome are more commonly poorly differentiated and are more commonly mucinous than sporadic CRCs. Despite these aggressive histologic traits, the overall 5-year survival rates are better than that seen in sporadic CRC. Patients treated with subtotal colectomy have a 45% chance of developing another colon cancer in the remaining colon.[200]

Lynch syndrome is associated with an increased risk of extracolonic cancers. Endometrial cancer is the second most common malignancy in women with Lynch syndrome, with a cumulative risk of 20 to 60%.[201–203] Recent studies have suggested that endometrial cancer risk may be greater than colon cancer risk.[204,205] The average age of onset of Lynch syndrome–associated endometrial cancers is in premenopausal women in their forties.[203,206,207] Lynch syndrome–associated endometrial cancers generally have favorable prognostic features including early stage and well-differentiated endometrioid histology, and a resultant 90% survival.[207,208] Endometrial cancer risk is highest for women with mutations in the *MSH6* gene (60 to 71%) with lower endometrial cancer risks associated with the *MLH1* and *MSH2* genes (27 to 60%).[205] Of note, endometrial cancers located in the lower uterine segment appear to have an association with Lynch syndrome.[205] Endometrial cancer in a non-obese young woman should raise suspicion that this might be due to Lynch syndrome.

In addition, Lynch syndrome carriers have an increased risk of ovarian, small bowel, stomach, pancreatic, ureteral, and renal cancers. Lynch syndrome–associated ovarian cancer cases represent approximately 1% of all ovarian cancers.[209] The lifetime risk of a Lynch syndrome carrier developing ovarian cancer is increased to 5 to 12%.[201–203] The age of onset of Lynch syndrome–associated ovarian cancers is in the early 40s, and the clinical features of the ovarian cancers are generally more favorable than sporadic cases.[203,204] Many of these cancers present at an early stage and about 20% of Lynch syndrome–associated ovarian cancers occur concurrently with endometrial cancer.[204] As with endometrial cancer, the risk of ovarian cancer is commonly associated with *MSH6* mutations.

The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer established research criteria for the diagnosis of Lynch syndrome; these were later modified and are referred to as the Amsterdam II criteria (see Table 21.8). These suggest that Lynch syndrome should be suspected when there is the Amsterdam criteria for the diagnosis of the syndrome.[199,210] These criteria include (a) histologically verified CRC in three or more relatives, one of whom is a first-degree relative of the other two, with exclusion of FAP; (b) Lynch syndrome–associated cancers involving at least two successive generations; and (c) at least one family member who has developed a Lynch syndrome–associated cancer before the age of 50 years. Many families meeting the Amsterdam criteria did not have an identifiable MMR gene mutation so the syndrome is usually defined using a genetic diagnosis. For those who meet criteria but do not have any of the known genetic mutations, it has been suggested to use the term "familial colorectal cancer type X" for them.[211]

In response to the low sensitivity of the Amsterdam criteria to identify families for whom genetic testing may be warranted, the Bethesda guidelines (see Table 21.9) were created. For patients who meet the criteria, it is recommended that they have their colon cancers tested for MSI and follow-up MMR gene testing if they do have high levels of MSI in their tumors. Relying on the Amsterdam or Bethesda criteria alone, however, may miss a large number of patients with Lynch syndrome.[212]

The Society for Gynecologic Oncologists (SGO) have created guidelines to help clinicians identify patients who may benefit from hereditary cancer risk assessment for breast, ovarian, and endometrial cancer predisposition associated with Lynch syndromes. The SGO recommends that individuals whose risk of having an inherited predisposition to cancer greater than approximately 20 to 25% ***should*** undergo genetic risk assessment. However, it is also reasonable to offer genetic risk assessment to any individual with greater than approximately 5 to 10% chance of having an inherited predisposition to cancer (see Tables 21.10 and 21.11 for identification criteria of women with greater than 20 to 25% inheritance risk and 5 to 10% inheritance risk, respectively).[213] Some centers have moved towards a universal MSI testing approach for all endometrial cancers, although this has not yet been proven to be more cost effective than assessment based upon family history.[213a]

TABLE 21.8 Amsterdam Criteria

Revised Amsterdam Criteria by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer
There should be at least three relatives with an HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
One should be a first degree relative of the other two
At least two successive generations should be affected
At least one should be diagnosed before age 50 years
Familial adenomatous polyposis should be excluded in the colorectal cancer case(s) if any
Tumors should be verified by pathological examination

HNPCC, hereditary nonpolyposis colorectal cancer.
Adapted from Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (NPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology.* 1999;116:1453–1456.

TABLE 21.9 Bethesda Guidelines for Testing Colorectal Tumors for Microsatellite Instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors,[a] regardless of age.
3. Colorectal cancer with the MSI-H[b]–like histology[c] diagnosed in a patient who is less than 60 years of age.[d]
4. Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

[a]Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.
[b]MSI-H: microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute–recommended panels of microsatellite markers.
[c]Presence of tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.
[d]There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.
From Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst.* 2004;96:261–268. Copyright © 2004 Oxford University Press.

Diagnosis of Hereditary Colon Cancer

With the identification of genes responsible for hereditary colon cancer, families suspected of having familial colon cancer can now undergo genetic testing. Many of the issues that were discussed with regard to *BRCA1*

TABLE 21.10 Patients With Greater Than Approximately 20–25% Change of Having An Inherited Predisposition to Endometrial, Colorectal, and Related Cancers and For Whom Genetic Risk Assessment Is Recommended

- Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria as listed below:
  - At least 3 relatives with a Lynch/HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis) in one lineage;
  - One affected individual should be a first degree relative of the other two;
  - At least 2 successive generations should be affected;
  - At least 1 HNPCC-associated cancer should be diagnosed before age 50.
- Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50
- Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50
- Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e. microsatellite instability (MSI) or immunohistochemical loss of expression of MLH1, MSH2, MSH6 or PMS2)
- Patients with a first or second degree relative with a known mismatch repair gene mutation

From Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol.* 2007;107(2):159–162.

and *BRCA2* testing in families with breast and ovarian cancer apply to genetic testing for hereditary colon cancer. Pedigrees should be thoroughly documented, and the other critical steps in the genetic counseling process must occur.

Women in FAP families should be offered testing for FAP gene mutations, preferably after identification of a mutation in an affected family member. A founder mutation of the FAP gene has been identified in 6% of Ashkenazi Jews (T to A in codon 1307). Although the polymorphism does not affect the function of the APC protein, it creates a stretch of eight adenine bases that is highly susceptible to inactivating mutations. Affected individuals appear to have about a 20% lifetime risk of CRC. Although the penetrance of this FAP polymorphism is lower than that of clearly deleterious FAP mutations, because the polymorphism is much more frequent, it is estimated to be responsible for about 28% of familial CRC in the Ashkenazi population.[214,215]

TABLE 21.11 Patients With Greater Than Approximately 5–10% Change of Having An Inherited Predisposition to Endometrial, Colorectal, and Related Cancers and For Whom Genetic Risk Assessment May Be Helpful

- Patients with endometrial or colorectal cancer diagnosed prior to age 50
- Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/HNPCC-associated tumor* at any age
- Patients with endometrial or colorectal cancer and a first degree relative with a Lynch/HNPCC-associated tumor* diagnosed prior to age 50
- Patients with colorectal or endometrial cancer diagnosed at any age with two or more first or second degree relatives† with Lynch/HNPCC-associated tumors*, regardless of age
- Patients with a first or second degree relative† that meets the above criteria

*Lynch/HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel.
†First and second degree relatives are parents, siblings, aunts, uncles, nieces, nephews, grandparents and grandchildren.
From Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol.* 2007; 107(2):159–162.

Although mutations in the FAP gene are responsible for 70 to 80% of FAP syndrome, some families have colorectal polyposis without a mutation in the FAP gene. In these families, an autosomal recessive inheritance of the *MYH* gene is probable.[216] As an autosomal recessive gene, expression of the cancer syndrome requires mutation in both copies of the *MYH* gene.

In families suspected of a hereditary CRC syndrome that is not FAP, the previously described Amsterdam criteria requiring at least one family member with a diagnosis of colon cancer at an early age and at least three affected individuals in two contiguous generations serves as a reasonable guideline for selecting candidates for genetic testing. A consensus conference of the NCI in Bethesda developed guidelines for screening of cancer patients with suspected inherited CRCs.[217] These guidelines call for MSI testing in the following cases: CRC diagnosed at age younger than 50 years; CRC with synchronous or metachronous CRC or extracolonic Lynch syndrome–associated tumors, independent of age; CRC with microsatellite instability-high (MSI-H) histology at age younger than 60 years; CRC in patient with one or more first-degree relatives with Lynch syndrome related tumor, with one tumor younger than 50 years of age; or CRC in a patient with two or more first- or second-degree relatives with Lynch syndrome–related tumors, age independent.[218] The NCI screening strategy uses MSI in tumor DNA because MSI is present in most colon and endometrial cancers that arise in individuals who inherit mutations in the DNA repair genes. If MSI is found, the specific DNA repair genes are then screened for mutations. One drawback to this approach is that sporadic colon and endometrial cancers may have MSI due to silencing of the *MLH1* gene by promoter methylation.[219] Another approach to screening for Lynch syndrome is to perform immunohistochemical staining for MMR proteins such as *MSH2* and *MLH1* in the cancers.[219] Loss of expression of one of the proteins is then followed by MSI testing and/or gene sequencing to identify a mutation.

Computerized algorithms exist for prediction of the carrier risk of Lynch syndrome (Myriad, Barneston, Wijnen, MMRpro, PREMM). These computerized algorithms were validated for probands with colorectal cancer but may also be valid for Lynch syndrome

probands presenting with endometrial cancer.[220] Despite development of risk predictive programs, MSI testing and sequencing of MMR genes remains the gold standard in genetic testing.[221,222] Other molecular tests are being developed in hopes of streamlining the laborious process of sequencing Lynch syndrome genes.[223] Lynch syndrome–related cancers outside of the colon are more common with mutations in *MSH2* and *MSH6*, whereas *MLH1* and *MSH2* confer more CRC risk.[204] Up to 27% of Lynch syndrome patients may carry a large genomic deletion of the *MSH2* gene.[224] Founder mutations can be detected in Lynch syndrome families from particular geographic or ethnic backgrounds. Ashkenazi Jewish Lynch syndrome families are at risk of carrying the *MSH2* A636P or 1906G→C mutations.[219,225] One mutation in *MSH2* (c.942+3A→ T) may account for 5 to 10% of all Lynch syndrome cases in the world, with a particularly high representation in Newfoundland Lynch syndrome families.[219] In Finnish Lynch families, a genomic deletion of exon 16 is carried by 50%.[219] In the United States, the American Founder Mutation (AFM) consists of a large genomic deletion of exons 1 to 6 of *MSH2*.[219]

Once a mutation is detected, testing can be offered to all family members. In view of the high penetrance of these mutations (approximately 90%), every effort should be made to identify all of the carriers within a family. Identification of HNPCC mutations and genetic testing reduces the number of colon carcinomas and extracolonic malignancies, such as endometrial and ovarian cancer, and reduces mortality.[192,226]

Hereditary Colon Cancer Surveillance and Treatment

Current recommendations for colon cancer surveillance in Lynch syndrome patients begin with genetic counseling at age 20 years (see Table 21.12 for surveillance recommendations for Lynch syndrome carriers). A full colonoscopy should be performed every 1 to 2 years starting at age 20 to 25 years, or at least 10 years earlier than the youngest affected family member.[190] The ACG recommends colonoscopy every 2 years beginning at age 20 to 25 years, until age 40 years, then annual colonoscopy.[186] Colonoscopy rather than sigmoidoscopy is appropriate because most of the colon cancers in this syndrome are right-sided.[192] If cancer is found, at least a subtotal colectomy is indicated. Patients found to have an adenoma on colonoscopic screening are advised to undergo surgery because colonoscopic polyp resection is often inadequate with these broad-based lesions. In addition, patients who develop adenomas have a substantial risk of recurrent polyps and cancer formation. Patients with Lynch syndrome can develop invasive lesions from adenomas in as little as 2 years, in contrast to the general population where this transition is believed to require 8 to 10 years. For this reason, surveillance intervals should not be longer than 2 years apart.[227]

Patients in FAP families should undergo genetic testing between ages 10 and 12 years, if possible. If genetic testing is not possible, current recommendations suggest yearly sigmoidoscopy or colonoscopy from age 12 years until total colectomy is performed.[186,199] Frequent endoscopic screening of the upper GI tract, including the stomach, duodenum, and periampullary region, is recommended.[199]

Surgical prophylaxis for hereditary colon cancer varies by the syndrome type. FAP mutation carriers generally should undergo prophylactic total colectomy.[199] Half of FAP patients will develop colon cancer by age 40 years, and all develop cancer by age 70 years.[200] Prophylactic colectomy with ileorectal anastomosis is a reasonable option for asymptomatic Lynch syndrome mutation

TABLE 21.12 Surveillance Recommendations for Lynch Syndrome Carriers

Test	Age at Initiation	Frequency
Colonoscopy[a]	20–25 yr, or 10 yr prior to the earliest age of colon cancer diagnosis in the family (start at age 30 yr if family has *MSH6* mutation)	Every 2 yr until age 40 yr; annually thereafter
Endometrial sampling	30–35 yr, or 5–10 yr earlier than the earliest age of the first diagnosis of these cancers in the family	Annually with discussion of risk-reducing hysterectomy after age 35 yr or when childbearing is complete
Transvaginal ultrasound, CA 125 level	30–35 yr, or 5–10 yr earlier than the earliest age of the first diagnosis of these cancers in the family	Annually with discussion of rrBSO after age 35 yr or when childbearing is complete
Gastroscopy	30–35 yr	1–2 yr
Urinary bladder ultrasound	30–35 yr	1–2 yr
Urine cytology	25–35 yr	Annually

[a]Subtotal or total colectomy is indicated when a polyp or cancer is found.

Adapted from Lindor NM, Peterson GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA*. 2006;296(12):1507–1517; Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2008. *Am J Gastroenterol*. 2009;104:739–750.

carriers.[199,228] Patients who have only segmental colectomy are at increased risk for subsequent adenoma or colonic cancer formation in the remaining colon compared to those who have total colectomy with ileorectal anastomosis.[229] The retained rectum remains at risk for cancer, and flexible sigmoidoscopy is recommended every 6 to 12 months.[186] The choice between close surveillance and prophylactic surgery is one that each carrier must decide for himself or herself after nondirective counseling.

A low-fat and high-fiber diet with lots of fruits and vegetables is associated with a decreased incidence of CRC in the general population. However, it is not known whether dietary interventions would decrease the incidence of cancer in Lynch syndrome families. There is some evidence that chemoprevention with sulindac (a nonselective COX-1 inhibitor), or celecoxib (a selective COX-2 inhibitor) reduces adenoma development in some APC carriers.[230,231]

Management of the Risk of Endometrial and Ovarian Cancers in Women With Lynch Syndrome

Due to the increased risk of endometrial cancer in Lynch syndrome families, yearly endometrial sampling is suggested beginning at ages 30 to 35 years or 5 to 10 years prior to the earliest age of first diagnosis of Lynch-associated cancer of any kind in the family, whichever comes first.[1,232,233] Annual endometrial biopsy was shown to be superior to annual transvaginal ultrasound in detection of endometrial disease in women with Lynch syndrome.[234] However, the efficacy of this approach in reducing mortality remains unproven because most Lynch syndrome–associated endometrial cancers are diagnosed at an early, highly curable stage when they present with abnormal uterine bleeding.

Although pelvic exam, ultrasound, and serum CA 125 levels every 6 to 12 months, starting at ages 30 to 35 years or 5 to 10 years prior to the earliest age of first diagnosis of Lynch-associated cancer of any kind in the family, whichever comes first, have been advocated for ovarian cancer screening in Lynch syndrome families, the use of these techniques for diagnosing ovarian cancer while it is still confined to the ovaries is unproven.[235] Chemoprevention of endometrial and ovarian cancer with oral contraceptives is not contraindicated, although there is no supporting evidence for this approach in Lynch syndrome.[205]

Prophylactic hysterectomy and BSO should be considered in patients undergoing colectomy if childbearing has been completed. Ideally, concurrent hysterectomy, BSO, and any necessary surgical staging will have been planned in advance with both the general surgery team and gynecology team. Intraoperative opening and examination of the uterus is important, especially if a preoperative endometrial biopsy has not been obtained. Some Lynch syndrome mutation carriers will decline colectomy in favor of periodic colorectal cancer screening due to quality-of-life issues after colectomy. In these patients, prophylactic hysterectomy and BSO can be offered in view of the increased risks of uterine and ovarian cancer, but there is not strong evidence that this reduces mortality. Treatment of surgical menopause symptoms with hormone replacement therapy is not contraindicated in Lynch syndrome patients.[205]

FUTURE DIRECTIONS

Gynecologists have an important role in the identification of high-risk patients through the assembly of family history and pedigrees, as well as referral for genetic testing. Increasingly, risk-reducing surgery and chemoprophylaxis are part of the gynecologists' arsenal in these families as we strive to reduce mortality from the hereditary breast, ovarian, colon, and endometrial cancers. Most of the high-penetrance genes responsible for hereditary cancers likely have been discovered. Additional very rare genetic variants that are associated with a high lifetime cancer risk may be discovered in the future. Extensive sequencing efforts of individual genomes will be required to identify these variants.

Finally, there is good evidence that common genetic variants exist that increase cancer risk slightly (10 to 50%), but due to the high frequency of these variants, they may account for a significant fraction of cancers. Because these genetic polymorphisms only increase risk slightly, they do not cause recognizable familial cancer clusters. There are about 10 million common polymorphisms in the genome for which the rare allele has a frequency greater than 10%. Candidate gene and genome-wide association studies of ovarian cancer have revealed the existence of several genetic polymorphisms that alter risk by 10 to 40%.[236,237] Many of these genetic polymorphisms discovered by genome-wide scans are not within genes and may represent markers linked to the actual causative mutations. Testing for low-penetrance genetic polymorphisms that predispose to breast and prostate cancer is commercially available, but such testing has not yet been shown to have clinical use in reducing cancer mortality.[17] In the future, it may be possible to define moderate risk groups based on a panel of genetic polymorphisms along with epidemiologic risk factors. This would allow screening and prevention strategies to be focused on those most likely to benefit from these interventions. This could be desirable from a cost-effectiveness standpoint, particularly in relative rare diseases such as ovarian cancer that have a high mortality rate.

CLINICAL NOTES

- Up to 10% of certain cancer types appear to have a strong heritable component.
- Cancers of the colon, breast, and ovary are the most common hereditary cancers in women; it is believed that 5 to 10% of these cancers have a hereditary basis.
- Cancer results from loss of growth regulatory controls and DNA repair mechanisms.
- When caring for a patient or family with hereditary cancer, a thorough cancer family history is absolutely essential. Data on all maternal and paternal first- and second-degree relatives must be obtained. Other extended family history should be recorded, if available.
- Ten percent of breast and ovarian/fallopian tube cancers are due to autosomal dominant hereditary syndromes. Most hereditary ovarian cancer cases are due to germline mutations in *BRCA1* and *BRCA2*. At least half of hereditary breast cancers are due to germline mutations in *BRCA1* and *BRCA2*.
- In families with *BRCA1* mutations, the lifetime risk of breast cancer by age 70 years is about 65%, and the lifetime risk of ovarian cancer is about 25 to 50%. The incidence of prostate, colon, pancreatic, and stomach cancers may also be increased.
- In families with *BRCA2* mutations, the elevated lifetime risk of breast cancer approximates the risk seen in families with *BRCA1* mutations, but the lifetime risk of ovarian cancer is 10 to 20%.
- The probability of finding a *BRCA1* or *BRCA2* mutation in a woman older than age 50 years who is the only individual in her family with ovarian or breast cancer is less than 3%.
- Prior to genetic testing, all women should receive counseling explaining the postulated risks and benefits before deciding to undergo testing. Direct-to-consumer genetic testing that does not include counseling should be discouraged. Confidentiality remains a critical issue in cancer susceptibility testing, however, passage of the Genetic Information Nondiscrimination Act (GINA) has provided the protection of federal law.
- rrBSO for carriers of *BRCA1* or *BRCA2* mutations is an attractive option because it can be done using minimally invasive surgery, usually only causes modest changes in body image or self-esteem, and costs are generally covered by medical insurance. It does not guarantee that a subsequent peritoneal malignancy will not develop, although this rarely occurs. Hysterectomy at the time of rrBSO may be considered.
- Prevention of breast cancer in *BRCA1* and *BRCA2* carriers is more complex. Mastectomy causes marked alterations in body image and self-esteem, even with breast reconstruction. Total mastectomy is recommended because cancer may form in the nipple if it is not removed. There is still no guarantee with total mastectomy that all breast tissue will be excised.
- Close surveillance with frequent mammography, breast MRI, and clinical breast examinations are recommended starting in the 20s for *BRCA* carriers.
- Colon cancer is the third most common cause of cancer mortality in American women.
- Familial APC syndrome is an autosomal dominant trait and accounts for about 1% of all colon cancers. Individuals with APC mutations should undergo prophylactic total colectomy because half of these patients will develop colon cancer by age 40 years, and all develop cancer by age 70 years.
- A polymorphism in the gene associated with FAP affects approximately 6% of all Ashkenazi Jews. Affected individuals have a 20% lifetime risk of colon cancer.
- The most common form of hereditary colon cancer is HNPCC, or Lynch syndrome, which accounts for about 5 to 10% of CRCs. There are three clinical criteria for this diagnosis: CRC in three or more relatives with one being a first-degree relative of the other two, CRC in two successive generations or more, and one family member who developed CRC by age 50 years.
- Patients with mutations in the *MLH1*, *MSH2*, *MSH6*, or *PMS2* genes are at risk for Lynch syndrome–related cancers. They should undergo genetic counseling at age 20 years, and a full colonoscopy should be done every 2 years until age 35 years and then annually thereafter.
- Risks for uterine cancer in women from Lynch syndrome families exceeds that of colon cancer. Women in Lynch syndrome families should consider undergoing yearly endometrial biopsy starting at age 30 years. Consideration should be given to risk-reducing hysterectomy after completion of childbearing.

  Lynch syndrome also confers an increased risk of ovarian cancer. Annual screening with transvaginal ultrasound and CA 125 should be considered. Risk-reducing salpingo-oophorectomy should be considered in conjunction with hysterectomy after completion of childbearing.

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CHAPTER 22

Occupational and Environmental Exposures

Patrice Sutton, Joanne L. Perron, Linda C. Giudice, and Tracey J. Woodruff

INTRODUCTION

The fact that exposure to chemicals can harm human reproduction has been known since Roman times, when lead was first recognized to cause miscarriage and infertility in women and men.[1,2] Over the past 60 years, it has become clear that the placenta does not protect the fetus from damaging chemicals,[3] that the fetus can be uniquely sensitive to chemical exposures,[4,5] and that intergenerational harm can result from in utero chemical exposures (Table 22.1).[6,7] These discoveries stemmed from exposure to drugs and higher levels of environmental chemical exposure than typically encountered by the general population. Until recently then, it was generally assumed that environmental exposures experienced by an average person living in the United States would be below levels of reproductive harm, that is, hazards that effect fertility, conception, pregnancy, and/or delivery.

A rapidly expanding body of scientific evidence has upended this assumption about the benign nature of "low-level" environmental exposures.[7,8] For example, studies have demonstrated that the levels of chemicals that an average person is exposed to can perturb biological processes, such as preventing genes from functioning normally and interfering with the hormonal regulation critical to healthy reproduction.[9,10] We now know that the human reproductive system is vulnerable to such biological perturbations, particularly when these changes occur during critical windows of development (Fig. 22.1). Even subtle perturbations caused by chemical exposures may lead to important functional deficits and increased risks of disease and disability in infants, children, and across the entire span of human life.[11–13]

ADVERSE TRENDS IN REPRODUCTIVE HEALTH

Scientific evidence of declining reproductive function and increasing rates of reproductive illnesses since the mid-20th century that suggest our reproductive health and, ultimately, our reproductive capacity are under strain.[11,13–15] A spectrum of female and male reproductive disorders as well as poor birth outcomes and childhood disorders are increasing. (See Table 1 in reference 16 for a wide range of examples that exemplify adverse trends.)[16] From 1990 to 2005, birth weight decreased among term births in the United States, and these declines were not explained by trends in maternal and neonatal characteristics, changes in obstetrical practices, or concurrent decreases in gestational length.[17] There is increasing data that some aspects of human male reproductive health is declining and may be associated with exposure to a range of hormonally active toxicants.[18–19] Some of these effects include declines in serum testosterone levels over several decades, declines in sperm counts, and a shortened anogenital distance (seen after exposure to certain phthalates).[19–21] The evidence of impact from even low-level environmental exposures found in studies of laboratory animals and human populations is further amplified by signals from wildlife populations showing altered reproductive performance in annelids, mollusks, crustaceans, insects, fish, amphibians, and other mammals.[22,23]

HUMAN EXPOSURE TO TOXIC ENVIRONMENTAL CHEMICALS

These trends in reproductive health changes have occurred in roughly the same time frame in which human exposure to both natural and synthetic chemicals has dramatically increased. Approximately 87,000 chemical substances are registered for use in U.S. commerce as of 2006, with about 3000 chemicals manufactured or imported in excess of 1 million pounds each,[24] and approximately 700 new industrial chemicals are introduced into commerce each year.[25] These chemicals are distributed throughout homes, workplaces, and communities and are found in food, water, air, and consumer products. All women (including pregnant women), men, children, and infants in the United States have measurable levels of multiple environmental contaminants in their body (Table 22.4).[26,27]

The nature and extent of the relationship between these trends and environmental contaminants is rapidly unfolding. The strength of the evidence linking ubiquitous exposure to environmental contaminants to adverse health outcomes is sufficiently high that leading scientists and reproductive health and other clinical practitioners have called for timely action to prevent continued or future harm.[12,13,16,28,29]

TABLE 22.1 Examples of Human Evidence That Documents Key Principles in Reproductive Environmental Health

The placenta does not protect the fetus from damaging chemicals: Methylmercury

In the 1950s, methylmercury exposure *in utero* resulted in severe neonatal neurologic impairment in children after pregnant mothers consumed high levels of methylmercury in fish and shellfish contaminated from toxic industrial releases in Minamata, Japan. More recent evidence documents that developmental and cognitive effects can occur in children exposed prenatally to mercury at low doses that do not result in effects in the mother[a–c] and that the adverse neurologic effects of methylmercury exposure may be delayed.[d,e] As of 1992, there were 2252 officially recognized cases of Minamata disease.[f]

The fetus can be uniquely sensitive to chemical exposures: Thalidomide

In the 1960s, thalidomide, a drug given to pregnant women for morning sickness, with no adverse maternal consequences, resulted in a high rate of congenital limb and gastrointestinal malformations when taken during days 28–42 postconception. It is estimated that more than 10,000 children in 46 countries where the drug had been approved were born with deformities as a consequence of their mothers using the drug during pregnancy.[g]

Intergenerational harm can result from in utero chemical exposures: Diethylstilbestrol

Diethylstilbestrol (DES), which was prescribed in up to 10 million pregnancies from 1938 to 1971 to prevent miscarriage, was subsequently found to be a "transplacental carcinogen" causally linked to postpubertal benign and malignant reproductive tract abnormalities in the daughters and sons of DES-exposed mothers. These adverse health impacts manifested only decades after exposure. Established health impacts of in utero DES exposure include vaginal clear cell adenocarcinoma, vaginal epithelial changes, reproductive tract abnormalities (e.g., gross anatomical changes of the cervix, T-shaped and hypoplastic uteri), ectopic pregnancies, miscarriages, and premature births, and infertility in females exposed in utero; reproductive tract abnormalities (e.g., epididymal cysts, hypoplastic testis, cryptorchidism) in males exposed in utero; and increased risk for breast cancer in women who took the drug while pregnant.[h] Recent cohort studies indicate that women who were exposed to DES prenatally have an increased risk of breast cancer after age 40 years.[i] Animal data predict intergenerational impacts (i.e., among granddaughters of DES-exposed women) that is supported to date by limited human data.[j]

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THE ROLE OF CLINICIANS IN PREVENTION

Clinicians caring for women of childbearing age are uniquely poised to prevent or identify possible harmful exposures to toxic environmental contaminants and must be able to respond to questions as well as advise patients about the (preventable) health impacts incurred by exposure to toxic substances.[16] The embryo, fetus, and developing human are highly vulnerable to exposure to even small amounts of environmental toxicants,[12,13,28] due to their high metabolic rate, underdeveloped liver-detoxifying mechanisms, and immature

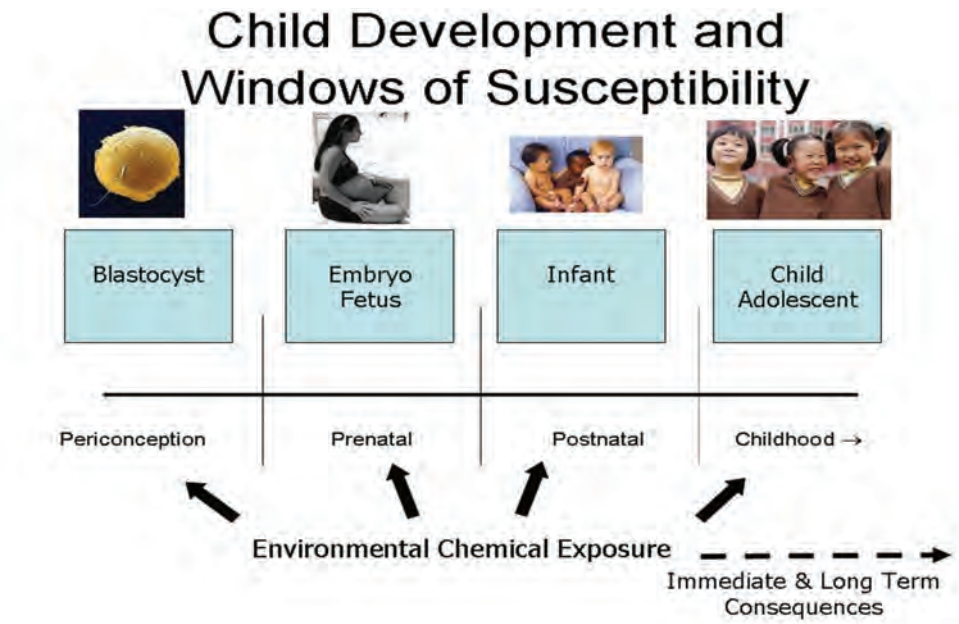

FIGURE 22.1 Windows of susceptibility. (Modified from Buck Louis GM, Gray LE Jr, Marcus M, et al. Environmental factors and puberty timing: expert panel research needs. *Pediatrics*. 2008;121[suppl 3]:S192–S207.)

immune system and blood–brain barrier.[30] Reducing or eliminating exposure to environmental contaminants *prior* to conception is the most effective strategy for preventing adverse health consequences. Clinicians do not need to become experts in environmental and occupational health in order to fulfill this crucial role.

This chapter presents an overview of the nature and extent of the scientific evidence linking exposures to environmental toxicants to reproductive and developmental health outcomes. It also outlines clinical management strategies for the general patient population and for the occupationally exposed patient, presents a case study for counseling patients about an environmental exposure, and provides other practical information for clinicians to assist them in addressing this important, and often overlooked, determinant of patient health.

DEFINITIONS

Reproductive Environmental Health

"Reproductive environmental health" addresses exposures to environmental contaminants (synthetic chemicals and metals), particularly during critical periods of development (such as prior to conception and during pregnancy), and their potential effects on all aspects of future reproductive health throughout the life course, including conception, fertility, pregnancy, child and adolescent development, and adult health.[13] Reproductive environmental health is thus an important area of intervention for clinicians caring for patients with reproductive capacity.

Environmental Contaminants

Environmental contaminants include heavy metals and synthetic chemicals in air, water, soil, food, and consumer products, and found in the home, community, and workplace environment, such as pesticides, solvents, air pollution components, and persistent organic pollutants. Exposures causing reproductive harm may be physical forces (e.g., radiation, heat, excessive vibration), biological factors (e.g., viruses, parasites), or toxic agents. Toxicants may impact a fetus via direct maternal exposure during the pregnancy, or through effects that persist from previous maternal exposures (e.g., mobilization of stored toxicants from maternal fat or bone stores).

Critical and Sensitive Windows of Susceptibility

A critical *window of susceptibility* is a unique time period during development when exposures to environmental contaminants can disrupt or interfere with the physiology of a cell, tissue, or organ.[12] Exposures during this window may result in adverse, permanent effects that can have lifelong and even intergenerational impacts on health. Exposures during critical windows have specific effects on development; exposure to the same agent outside the critical window may incur different or no effects. In contrast, during a sensitive *window of susceptibility*, exposures may still affect development or result in eventual adult disease but with reduced magnitude compared with the effect of exposure during other time periods.[31] Given that development continues after birth, critical and sensitive windows are seen during periconception, pregnancy, infancy, childhood, puberty, pregnancy, and lactation (see Fig. 22.1).

Stage-specific effects of ethylene oxide used for sterilizing medical supplies and in manufacturing are illustrative of how the timing of exposure matters to whether and what adverse health outcome(s) arise. Ethylene oxide can induce skeletal effects when administered to mice at the zygote stage of development—long before skeletogenesis begins.[32,33] The spectrum of skeletal effects observed after exposure at the zygote stage differs from those observed after exposure during organogenesis.

Recent research into the mechanisms of toxicity of the pesticide chlorpyrifos, which can inhibit cholinesterase inhibitor and thus is neurotoxic, is also illustrative of this new paradigm. The conventional view of neurotoxicity from chlorpyrifos involves the metabolism of the molecule by the liver to the chlorpyrifos oxon, which causes an irreversible inhibition of acetylcholinesterase. However, animal studies by Slotkin and colleagues demonstrated that effects of chlorpyrifos on the developing brain are subtle, widespread, and can occur below the threshold for any signs of exposure, and even without any detectable cholinesterase inhibition.[34,35] Moreover, these studies have shown that chlorpyrifos disrupts rat brain development through a variety of cellular and molecular mechanisms, with both the mechanism and the outcome changing with the progression of cell differentiation.

The U.S. Environmental Protection Agency (USEPA) has not yet incorporated the implications of the critical nature of the timing of exposure into pesticide toxicity testing protocols. Data collected from manufacturers, the main source of USEPA data, often overlooks developmental, morphologic, and functional damage of fetal origin.[36]

Developmental Basis of Disease/Dysfunction

The Developmental Basis of Adult Disease/Dysfunction describes links between the in utero environment, the external environment, an individual's genes, and the propensity to develop disease or dysfunction later in life.[28] The central nervous system, the cardiovascular system, the endocrine system, and the immune system appear to be particularly vulnerable to adverse effects during early development, and specific diseases, such as particular cancer forms, may well be initiated before birth or during early postnatal life.[12]

Perinatal factors and their influences on the development of chronic adult disease was first described in the field of nutrition[38] with the evidence base independently evolving in the field of developmental toxicology.[30]

Animal studies clearly show that the in utero and neonatal developmental periods represent "critical windows" for nutrition and environmental exposures to impact later development.[40] Other important features about the developmental origins of disease and dysfunction paradigm are:

- The initiating in utero environmental insult can act alone or in concert with other environmental stressors;
- There is a range of potential effects and latencies (including the potential to affect future generations);
- Aberrant developmental programming can permanently alter gland, organ, or system potential;
- Altered gene expression or altered protein regulation likely play a role in the toxicant or nutritionally induced pathogenic responses.[39,40]

One example of the developmental origins of disease/dysfunction paradigm of practical import to the practicing clinician is the hypothesis that in addition to the impact of maternal nutrition on fetal growth, environmental endocrine disrupting chemicals can act as "obesogens" that can permanently derange developing regulatory systems required for body weight homeostasis.[40,41] Paradoxically, our food system contributes to virtually all of the fetal and developmental chemical exposures linked to obesity that were cited in the May 2010 White House Task Force on Childhood Obesity Report to the President,[42] including Bisphenol-A, perfluorooctanoate (PFOA), phthalates, fructose, and certain organophosphate pesticides.

PATIENT EXPOSURE TO ENVIRONMENTAL CONTAMINANTS

Chemical Agents

Synthetic chemicals and metals linked to reproductive, fertility, and/or developmental health effects are distributed throughout homes, workplaces, and communities, and contaminate food, water, air, and consumer products.[43] For example, certain chemicals in commonly used plastics[44] and persistent pesticides[45,46] share the ability to alter the endocrine, neurologic, and/or other biological systems. Plastics and pesticides are only two of the many chemical exposures encountered in daily life. Over 10,000 ingredients are used in personal care products; nearly 90% of these ingredients have not been evaluated for safety by any publicly accountable institution. People apply an average of 126 unique ingredients on their skin daily.[47] Table 22.2 lists examples of common contaminants, sources, and exposure circumstances linked to adverse reproductive, fertility, and/or developmental health outcomes.

Population-based studies conducted by the U.S. Centers for Disease Control and Prevention (CDC) demonstrate ubiquitous exposure to many chemicals found in homes, communities, and workplaces that can disrupt the normal functioning of hormones and cause other toxicities.[26,27] An analysis of CDC population-based biomonitoring data among pregnant women in the United States found virtually all pregnant women have body burdens of lead, mercury, toluene, pesticides, perchlorate, BPA, phthalates, perfluorochemicals (PFCs), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) (Table 22.3). Analysis of second-trimester amniotic fluid samples from 51 women found the presence of at least one environmental contaminant.[48] In some cases, such as for mercury, fetal exposures to environmental contaminants may be higher than maternal.[49–51] A 2013 report by CDC found mercury was present in 83% of U.S. women of childbearing age.[52]

Physical and Biological Agents

Although the focus of this chapter is occupational and environmental exposure to chemical agents, the practicing clinician needs to be aware that patient exposure to physical and biological agents can also impact health, including reproductive health. For example, shift work, that is, exposure to "light-at-night" involving circadian disruption, is associated with breast cancer in human studies, and, on the basis of human and animal evidence, has recently been classified by a Working Group of the International Agency for Research on Cancer as "probably carcinogenic to humans" (Group 2A).[53] Exposure to physical hazards such as ionizing radiation and biological hazards such as blood-borne pathogens are also of relevance to reproductive health practitioners, particularly among those with patients working in the health care sector.

THE EVIDENCE STREAM SUPPORTING CLINICAL DECISION MAKING RELATED TO ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

The evidence stream and decision context in environmental health sciences is quite different from that of clinical science and practice (Fig. 22.2).[54] Clinicians cannot assume as they do with pharmaceuticals that adequate in vitro and in vivo testing has been undertaken and considered by regulatory agencies before widespread human exposure to environmental contaminants occurs. Just because a product is readily available on the shelf at the store is no assurance that it is nontoxic. The vast majority of chemicals in commerce have entered the marketplace without comprehensive and standardized information on their reproductive or other chronic toxicities.[55] The inadequacies of the current regulatory framework are receiving increased attentions, and in 2009, the USEPA established "Essential Principles for Reform of Chemicals Management Legislation" to help inform legislative efforts now underway to reauthorize and significantly strengthen the effectiveness of chemical regulation.[55]

TABLE 22.2 Selected Examples of Contaminants Linked to Reproductive, Fertility, or Developmental Problems

Types of Contaminants and Examples	Sources and Exposure Circumstances
Metals	
Mercury	Occurs from energy production emissions and naturally. According to the U.S. EPA, coal-fired power plants are the largest current sources of mercury emissions in the country. Enters the aquatic food chain through a complex system. Primary exposure by consumption of contaminated seafood.
Lead	Occupational exposure occurs in battery manufacturing/recycling, smelting, car repair, welding, soldering, firearm cleaning/shooting, stained glass ornament/jewelry making; nonoccupational exposure occurs in older homes where lead-based paints were used, in or on some toys/children's jewelry, water pipes, imported ceramics/pottery, herbal remedies, traditional cosmetics, hair dyes, contaminated soil, toys, costume jewelry.
Organic compounds	
Solvents	Used for cleaning, degreasing, embalming, refinishing and paint systems in a wide range of industries. Found in automotive products, degreasers, thinners, preservers, varnish and spot removers, pesticides (inert component), and nail polish.
Ethylene oxide	Occupational exposure to workers sterilizing medical supplies or engaged in manufacturing.
Pentachlorophenol	Wood preservative for utility poles, railroad ties, wharf pilings; formerly a multiuse pesticide. Found in soil, water, food, and breast milk.
Bisphenol-A (BPA)	Chemical intermediate for polycarbonate plastic and resins. Found in consumer products and packaging. Exposure through inhalation, ingestion, and dermal absorption.
Polychlorinated biphenyls (PCBs)	Used as industrial insulators and lubricants. Banned in the 1970s, but persistent in the aquatic and terrestrial food chains resulting in exposure by ingestion.
Dioxins	Dioxins and furans are multiple toxic chemicals formed by trash and waste incineration involving chlorine and, as categorized as a persistent organic pollutants (POPs), pervasive chemicals which bioconcentrate as they move up the food chain. Found in dairy products, meat, fish and shellfish.
Perfluorochemicals (PFCs)	PFCs are widely used man-made organofluorine compounds with many diverse industrial and consumer product applications. Examples are perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), which are used in the manufacture of nonstick Teflon and other trademark cookware products and in food-contact packaging to provide grease, oil, and water resistance to plates, food containers, bags, and wraps that come into contact with food. Persist in the environment. Occupational exposure to workers and general population exposure by inhalation, ingestion, and dermal contact.
Polybrominated diphenyl ethers (PBDEs)	Flame retardants that persist and bioaccumulate in the environment. Found in furniture, textiles, carpeting, electronic, and plastics.
Di-(2 ethylhexyl) phthalate (DEHP), diethyl phthalate (DEP), di-n-butyl phthalate (DBP)	Synthetically derived; phthalates are used in a variety of consumer goods such as medical devices, cleaning and building materials, personal care products, cosmetics, pharmaceuticals, food processing, and toys. Exposure occurs through ingestion, inhalation, and dermal absorption.
Pesticides	Applied in large quantities in agricultural, community, and household settings. In 2001, over 1.2 billion pounds of pesticide active ingredients were used in the United States. Pesticides can be ingested, inhaled, and absorbed by the skin. The pathways of pesticide exposure include food, water, air, dust, and soil.
Chlorpyrifos	Organophosphate pesticide used in agricultural production and for home pest control (home uses are now restricted).
Dichlorodiphenyltrichloroethane (DDT)*	Organochlorine insecticide, banned in the United States in the 1970s, is still used for malaria control overseas. Present in the food chain.
Air contaminants	
Environmental tobacco smoke (ETS)	Burning of tobacco products. Exposure by inhalation from active or passive smoking.
Particulate matter (PM), ozone, lead	Sources include combustion of wood and fossil fuels, and industrial production. Exposure by inhalation.
Glycol ethers	Used in enamels, paints, varnishes, stains electronics, and cosmetics. Occupational and general population exposure by inhalation, ingestion, and dermal contact.

Note: Contaminants in *italics* are persistent and/or bioaccumulative.
Adapted from Fox MA. Environmental contaminants and exposure. In: Woodruff TJ, Janssen JS, Guillette LJ Jr, et al, eds. *Environmental Impacts on Reproductive Health and Fertility.* New York: Cambridge University Press; 2010.

Moreover, regulatory and medical ethical requirements dictate that human exposure to pharmaceuticals does not occur in the absence of some potential benefit greater than the known risks. The "gold standard" for informing clinical risk–benefit decisions about medical interventions is a well-conducted randomized controlled trial. There is no comprehensive comparable weighing of health benefits and risks in the environmental arena. Because of the shortcomings of the United States' current regulatory structure for governing manufactured chemicals population, exposure to exogenous substances in the environment typically occurs prior to regulatory scrutiny of a compound and in the absence of risk–benefit analyses. The benefits of environmental chemicals are largely unrelated to patient health, and exposures are generally unintentional and highly variable. Randomized controlled trials on environmental contaminants are virtually precluded from the evidence stream

TABLE 22.3 Percentage of U.S. Pregnant Women With Metals and Synthetic Chemicals Measured in Their Body*

Chemical Analyte	Percentage of U.S. Pregnant Women With Detectable Levels of the Analyte
Metals (blood; mcg/L) (*N* = 253)	
Cadmium	66
Lead	94
Mercury (total)	89
VOCs (blood; mcg/L) (*N* = 89)	
Benzene	38
1,4-Dichlorobenzene	40
MTBE (*N* = 85)	86
Toluene (*N* = 90)	94
PFCs (serum; mcg/L) (*N* = 76)	
PFOA	99
PFOS	99
PBDEs (serum; ng/g lipid) (*N* = 75)	
PBDE-47	99
PBDE-99	87
PBDE-100	99
PBDE-153	100
PCBs (serum; ng/g lipid) (*N* = 75)	
PCB-118	100
PCB-138 & 158	100
PCB-153	100
PCB-180	96
Organochlorine (OC) pesticides (serum; ng/g lipid) (*N* = 71)	
DDT	62
DDE	100
Hexachlorobenzene	100
Organophosphate (OP) insecticide metabolites (urine; mcg/L) (*N* = 89)	
Dimethylphosphate (DMP)	44
Diethylphosphate (DEP)	33
Dimethylthiophosphate (DMPT)	83
Diethylthiophosphate (DEPT)	57
Dimethyldithiophosphate (DMDTP)	56
Environmental phenols (urine; mcg/L) (*N* = 86)	
Bisphenol-A	96
Triclosan	87
Benzophenone-3	100
Phthalates (urine; mcg/L) (*N* = 91)	
Mono-n-butyl phthalate (MnBP)	99
Mono-ethyl phthalate (MEP)	100
Mono-benzyl phthalate (MBzP)	100
Mono-isobutyl phthalate (MiBP)	99
Perchlorate (urine; mcg/L) (*N* = 89)	
Perchlorate	100

DDT, dichlorodiphenyltrichyloroethane; DDE, dichlorodiphenyl dichloroethylene; VOCs, volatile organic compounds; MTBE, methyl-tert-butyl ether; PFC, perfluorochemical; PFOA, perfluoroctanoate; PFOS, perfluorooctane sulfonate; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl.

*Based on analysis of representative sample of U.S. population by the U.S. Centers for Disease Control and Prevention, National Health and Nutrition Examination Survey 2003–2004.

From Woodruff TJ, Zota A, Swartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. *Environ Health Perspect*. 2011;119(6):878–885.

due to ethical considerations. Therefore, when making decisions about patient exposure to environmental and occupational exposure to chemicals, clinicians must rely on in vitro and in vivo studies for early warnings of adverse effects and human observational studies to assess the nature and extent of the damage.

The reliability of experimental animal data for reproductive and developmental health has been well established through multiple studies of concordance between animals and humans after exposure to a variety of chemical agents.[56–60] Presently, there is no example of a chemical agent that has adversely affected human reproduction or development but has not caused the same or similar adverse effects in animal models.[58] The National Academy of Sciences (NAS) has recognized the importance of animal data in identifying potential developmental risks. According to the NAS, studies of comparison between developmental effects in animals and humans find that "there is concordance of developmental effects between animals and humans and that humans are as sensitive or more sensitive than the most sensitive animal species."[33] Biological function is conserved across animal species. Therefore, signals obtained from wildlife studies further strengthen the evidence seen in laboratory animals and human cell cultures.[61]

Human observational studies of environmental chemicals provide the most direct evidence of the relationship between exposure and increased risk of adverse health outcomes and are often the basis of regulatory and policy decision making. However, human epidemiologic studies require that we wait for people to develop clearly identified diseases from exposure and thus are not an optimal approach to clinical decision making. Whereas an experimental animal carcinogenic study typically lasts 2 years, it can take 20 years to get a result from a comparable human study.[62] For all of these reasons, the use of animal data and other non-human model systems is fundamental to timely prevention of adverse health outcomes in clinical decision making.

MECHANISMS OF ACTION

Epigenetic Mechanisms

The term "epigenetics" includes any process that alters gene activity and expression without mutating the DNA sequence and leads to modifications that can be transmitted

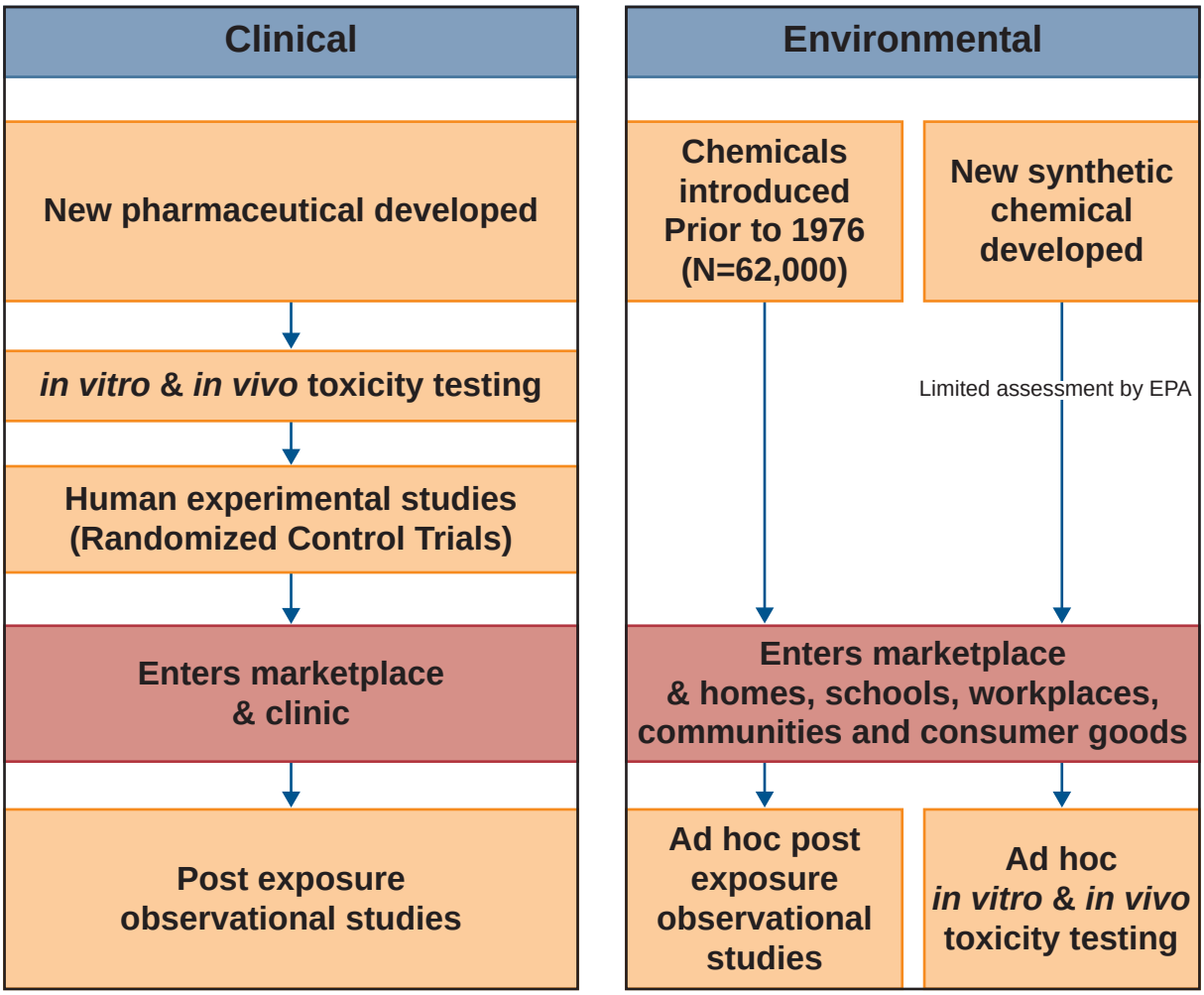

FIGURE 22.2 Comparison of streams of evidence in clinical and environmental health sciences.

to daughter cells.[63] Environmental modifications of gene expression can affect embryonic imprinting, cellular differentiation, and phenotypic expression.[64] The most common epigenomic alterations are methylation of the DNA at cytosine with subsequent gene silencing or modification of the DNA histone support, which affects chromatin folding and attachment. Tight folding inhibits gene expression and lithe folding allows gene manifestation.[64]

Illustrative of epigenetic mechanisms, in 2005, studies on laboratory animals began to establish a novel mechanism of action not previously appreciated on how pesticides and other environmental contaminants could act on a gestating mother to influence her grandchildren and subsequent generations.[65] Studies of male rats exposed to the fungicide vinclozolin demonstrated that epigenetic damage may be passed on to future generations. More recently, scientists have shown that female rats exposed to vinclozolin during a specific period of pregnancy exhibit a transgenerational increase in pregnancy abnormalities and female adult onset disease states.[66] These effects occurred after large doses were given and are not indicative of average occupational exposure to this pesticide. However, this study highlights the importance of performing transgenerational studies when evaluating the toxicology of environmental compounds.

Endocrine Disruption

Endocrine disruption is a related mechanism of action of environmental contaminants linked to increased risk for adverse reproductive health outcomes. The USEPA defines endocrine disruptors as compounds which "interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis (normal cell metabolism), reproduction, development, and/or behavior." This interference alters the function(s) of the endocrine system and may cause adverse health effects in an organism or its progeny or a (sub)population of organisms.[67] Endocrine disrupting compounds (EDCs) can act through traditional nuclear hormone receptor pathways (estrogen, progesterone, androgen, thyroid, and retinoid) and more diverse avenues such as nonnuclear, neurotransmitter, or orphan receptors and

enzymatic pathway interference.[28] The homeostasis of sex steroids and thyroid hormone are the main targets of EDCs. EDCs can directly interfere with ovarian steroid hormone production or alter the control and action of ovarian hormones at the level of the hypothalamic-pituitary-gonadal axis.[68] Indirect effects occur via the immune or nervous system, as well as through epigenetic transgenerational effects.[69,70] EDCs can have multiple hormonal effects, for example, BPA perturbs both estrogen and thyroid hormones.[71] Although EDCs are a broad and diverse group of agents, the molecular structures of EDCs often contain a central ring which mimics steroid hormones and often has added halogen groups (chlorine, bromine, fluorine),[28] which confer various material properties such as molecular stability. Examples of EDCs include persistent pollutants that may bioaccumulate (dioxins, cadmium) chemicals used in plant or food production, sex hormones from farm or urban waste that may become concentrated in urban or agricultural areas, or plant-derived hormonally active compounds. The general population is exposed on a daily basis to multiple EDCs through a diverse number of exposure pathways.[26,27]

Mutagenic Mechanisms

DNA damage can adversely affect reproduction and development. A well-documented example is radiation-induced cancer due to exposure to ionizing radiation. It is generally believed that complex forms of DNA double-strand breaks are the most biologically important type of lesions induced by ionizing radiation, and these complex forms are likely responsible for subsequent molecular and cellular effects.[72] There is growing concern about the sharp rise in the use of computed tomography scans in medicine due to the nonnegligible radiation exposures involved, particularly for pediatric patients.[73]

REPRODUCTIVE HEALTH IMPACTS OF EXPOSURE TO ENVIRONMENTAL AND OCCUPATIONAL CHEMICALS

Reproductive Health, Fertility, and Pregnancy

A wide range of adverse reproductive and developmental health outcomes are linked to exposure to environmental contaminants including impacts on pregnancy outcomes, reproductive health and fertility, timing and progression of pubertal development, and the formation of cancers of the reproductive tract. In 2009, the Endocrine Society, the premier professional organization devoted to research on hormones and the clinical practice of endocrinology, composed of over 14,000 research scientists and physicians from over 100 countries, reviewed the evidence linking environmental exposure to EDCs to human health and concluded, "The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis."[28]

A recent assessment of the evidence by Slama and Cordier[74] based on human epidemiologic evidence for fetal loss, fetal growth, gestational length, complications of pregnancy, and congenital malformations found sufficient evidence for one or more of these adverse outcomes for atmospheric pollution, passive smoking, lead, mercury, perfluorooctane sulfonate (PFOS) and PFOA, glycol ethers, aromatic solvents, and low-dose ionizing radiation.

A 2010 review by Mendola and Buck Louis[68] described the current state of the science linking environmental contaminant exposures to adverse reproductive health outcomes according to the timing of exposure. Based on the available evidence, the two reproductive health endpoints most consistent with an intrauterine origin are abnormal pubertal timing and polycystic ovarian syndrome (PCOS).[68] Synthetic chemicals and metals linked to adverse impacts on pubertal onset and maturation include persistent halogenated organic chemicals such as PCBs, DDT/DDE, and brominated flame retardants, and, to a lesser extent, dioxin, hexachlorobenzene, endosulfan, and heavy metals.[75] Although Mendola and Buck Louis[68] concluded that the animal data looking at the association between PCOS and BPA was few and limited, more recent animal evidence was the first to report a link between neonatal exposure to high doses of BPA with development of PCOS-like abnormalities in adulthood.[76] The review found that other potential adverse impacts of in utero exposure to environmental contaminants included endometriosis (for which the impact of environmental contaminants are recognized), leiomyoma (the role of the exogenous estrogens here is speculative), and menopause (although research in this area is extremely limited).

Mendola and Buck Louis[68] summarized the human evidence for adult exposure to environmental contaminants and adverse reproductive health effects as follows:

- Menstrual and ovarian function: Many compounds that are implicated with disruption of menstrual or ovarian function are EDCs, and the data are suggestive but equivocal; the limitations of the evidence may reflect reliance on cross-sectional study designs and data that do not capture critical and sensitive windows of exposure.
- Endometriosis: There is limited but somewhat consistent human evidence that persistent endocrine active pollutants such as PCBs and phthalates may play a role in the risk for endometriosis among adults.
- Fertility and fecundity: Many environmental contaminants have been linked to conception delays, infecundity and/or spontaneous abortion, and studies of human exposure to pesticides provide some of the strongest evidence implicating environmental contaminants to reduced fertility and fecundity.

Breast Cancer

Human exposure to substances that cause mammary gland tumors in laboratory animals is widespread. As of 2007, 216 chemicals tested in animal cancer bioassays have been found to be associated with mammary gland tumors in at least one animal study (Fig. 22.3); 29 are produced in the United States at more than 1 million pounds per year; 35 are air pollutants; 25 have been associated with occupational exposures affecting more than 5000 women a year; and 73 have been present in consumer products or as contaminants of food.[77] Very few of the chemicals identified as animal mammary gland carcinogens or EDCs have ever been included in a human breast cancer study and the limited existing studies are often plagued by a lack of good measures of exposure.[78] A 2007 comprehensive review of the current human evidence by Brody and colleagues[78] found the available evidence supports an association between exposure to polycyclic aromatic hydrocarbons (PAH) (combustion products) and breast cancer in women with suboptimal DNA repair genetic variations and strong associations between exposure to PCBs and breast cancer in carriers of certain genetic variants. Brody and colleagues[78] also concluded the evidence regarding dioxins and organic solvents was sparse and methodologically limited but suggestive of an association.

Reproductive and Developmental Impacts of Commonly Encountered Environmental Contaminants

Lead

Heavy metals in general, and lead in particular, provide the strongest evidence linking environmental exposures to healthy reproductive function in women. Lead may enter the body through inhalation and/or ingestion, with accumulation in soft tissues, bones, blood, the liver, and kidneys. Lead may be mobilized from the bone(s) during pregnancy and lactation. Health effects of lead exposure include adverse effects on male reproductive function,[2] pubertal delay in females,[79] increased risk of spontaneous abortion, hypertension during pregnancy, impaired offspring neurodevelopment, and reduced fetal growth.[80] Lead's impact on the neurodevelopment of a fetus is most profound in the first trimester.[81] The use of maternal calcium supplements, iron, and/or zinc may decrease maternal blood levels during pregnancy.[82-84]

Pesticides

Pesticides have been detected in human urine,[85] semen,[86] breast milk,[87,88] ovarian follicular fluid,[89,90] cord blood,[91,92] and amniotic fluid,[48,93] and are prevalent in food,[94] water,[95] and homes.[96,97] Some pesticides can interfere with all developmental stages of reproductive function in adult females[79] and are associated with adverse outcomes that occur throughout the life course of males and females, including sterility in males, spontaneous abortion, diminished fetal growth and survival, and childhood and adult cancer.[98,99-102]

Solvents

Occupational solvent exposure has been associated with a low sperm count,[103] reduced overall semen quality,[104] impaired fertility in women,[105,106] and increased risk of spontaneous abortion with maternal occupational exposure to ethylene glycol.[98] Prenatal solvent exposure is associated with birth defects, and it is believed some

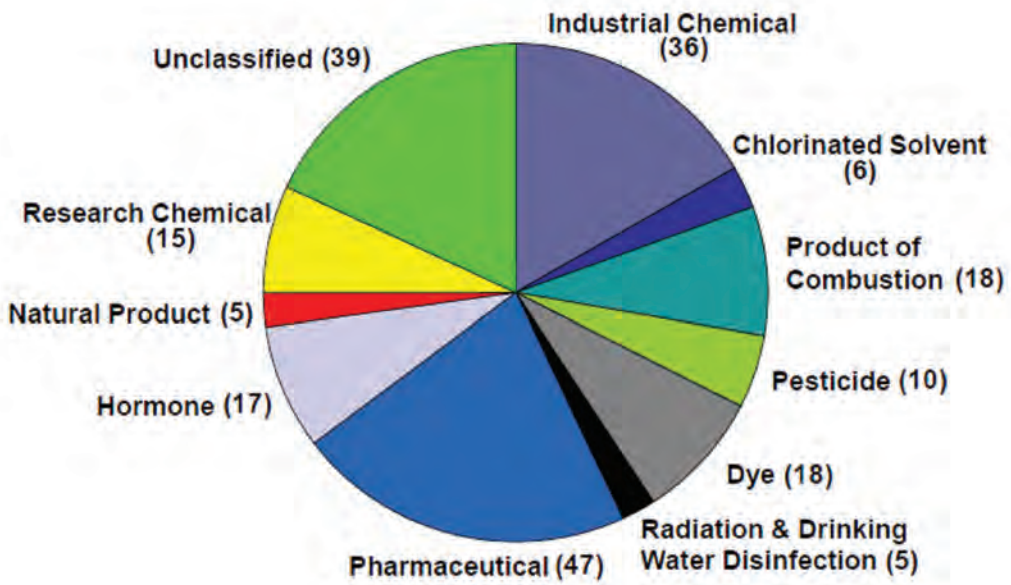

FIGURE 22.3 Sources of 216 chemicals that have been found to be associated with mammary gland tumors in at least one animal study. (From Rudel RA, Attfield KR, Schifano JN, et al. Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. *Cancer*. 2007;109[12][suppl]:2635–2666.)

organic solvents specifically increase the risk of congenital heart disease, low birth weight, or impaired fetal growth.[107–109]

Bisphenol-A

Bisphenol-A (BPA) is a monomer used to make hard polycarbonate plastics and some epoxy resins. Pregnant women are exposed to BPA at concentrations that are consistent with those shown to stimulate molecular targets in vitro and induce effects in laboratory animals in vivo.[71] In an evaluation of the reproductive and developmental effects of BPA by the National Toxicology Program (NTP), the authors report "limited evidence" of developmental toxicity at low doses and "clear evidence" of developmental toxicity at high doses, although they acknowledged "some concern" for neural and behavioral effects in fetuses, infants, and children at current BPA exposure levels.[110] Others contend that the evidence of low-dose effects in pregnancy is unequivocal[71] and qualitatively different than effects at high doses.[111] Thus far, the bulk of the evidence regarding low-dose effects has centered on animal models. Studies in animals show that exposure to BPA during critical windows of development can result in permanent alterations to the reproductive system in a number of ways, thus increasing the risk of future health problems, including rodent hematopoietic and testicular cancers as well as preneoplastic lesions of the breast and prostate.[112–114] BPA is an agonist for nuclear estrogen receptors—ER-α and ER-β.[115] BPA alters epigenetic programming of genes in experimental animals and wildlife. Specifically, prenatal and/or neonatal exposure to low doses of BPA results in organizational changes in the prostate, breast, testis, mammary glands, body size, brain structure and chemistry, and behavior of laboratory animals. There is also experimental animal evidence that adult exposure to BPA results in substantial neurobehavioral effects and reproductive effects in both male and female animal models. A central concern is that these adverse effects are occurring in animals within the range of exposure to BPA typical of the U.S. population.[116] Epidemiologic studies of BPA effects during pregnancy suggest numerous perturbations. There was a suggestive relationship between prenatal BPA exposure and higher birth weight in male and female infants.[117] There is concern that BPA exposures at current environmental levels may be associated with oocyte meiotic defects and consequently, recurrent miscarriages.[118] In a cross-sectional analysis of 45 patients with a history of three or more spontaneous abortions, researchers found higher circulating levels of antinuclear antibodies and BPA as compared to values measured in nonpregnant women with no history of miscarriages, although it is not possible to infer causal associations from this study.[119] A 2009 study found prenatal BPA exposure may be associated with externalizing behaviors in 2-year-old children, especially among female children.[120]

In the 2003 to 2004 National Health and Nutrition Examination Survey, approximately 93% of participants older than 6 years of age had evidence of BPA exposure on screening. The most common form of exposure is through dietary sources, and individuals may decrease exposure by not microwaving polycarbonate plastic food containers, using baby bottles that are BPA-free, avoiding use of plastic containers with no. 7 on the bottom, reducing the use of canned food, and opting for nonplastic serving or storage containers for hot food or liquids.[121] In late January 2011, the FDA banned the use of BPA in children's reusable food and beverage containers.

Dioxin

The developing individual is extensively sensitive to exposure to dioxin, with possible effects including alterations in thyroid and immune status; neurobehavioral changes affecting hearing, psychomotor function, and gender-related behaviors; changes in cognition, dentition, and reproductive organ development; delays in breast development, and altered sex ratios among exposed offspring.[122] Women exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after a 1976 industrial accident in Seveso, Italy, had a two-fold increased incidence of breast cancer associated with a 10-fold increase in serum levels of that chemical.[123] Seveso men exposed to TCDD prior to puberty had a reduction in sperm count and motility, whereas those exposed in adolescence had an increased sperm count and motility when compared to population norms. Both groups of men had permanent increased follicle-stimulating hormone (FSH) and decreased estradiol levels.[124] Dioxin exposures have been linked to intergenerational health impacts.[122,124]

Phthalates

Phthalates are found in soft, flexible plastics, polyvinyl chloride (PVC) products, some medical devices, flooring, personal care products, and other consumer products. Phthalates are measurable in most of the U.S. population including virtually every pregnant woman (Table 22.4).[125,126] Experimental animal studies show that exposure to some phthalates can cause reproductive damage. Because human exposure to phthalates is so widespread, these data raise serious concerns for human health.[44] Preliminary biological monitoring evidence among occupationally exposed populations has found significantly higher urinary metabolite levels of some of these toxic phthalates than the general public.[127] By inhibition of 5α-reductase,[128] phthalates perturb androgen mechanisms in rodents, creating a "phthalate syndrome" of numerous male reproductive abnormalities: infertility, decreased sperm count, shortened anogenital distance, hypospadias, cryptorchidism, and other malformations.[8,129] According to the NAS, phthalate syndrome has many similarities to the hypothesized

testicular dysgenesis syndrome in humans,[8] which asserts that perturbations during male reproductive development in utero can manifest in a constellation of future male reproductive health effects including poor semen quality, testicular cancer, cryptorchidism, and hypospadias.[130] A marker of this effect, decreasing anogenital distance, has been observed in animals and male infants prenatally exposed to phthalates.[8,129] In children, preconception phthalate exposure is associated with cognitive and behavioral disorders including altered play behavior in boys and diminished female neonatal motor skills.[131-133] Some studies have demonstrated a dose-response relationship between specific phthalates and low sperm concentrations, but not all investigators have seen this.[134-136] Europe has banned certain phthalates from cosmetics and baby toys, and some companies are voluntarily removing some common phthalates from their products.

Polychlorinated Biphenyls

Recent research indicates that current exposure levels to polychlorinated biphenyls (PCBs) and chlorinated pesticides can affect thyroid function during pregnancy. Chevrier and colleagues[45] found a statistically significant inverse relationship between levels of thyroid hormones and PCBs and organochlorine pesticides in pregnant women. As maternal T4 is the only source of thyroid hormone during the first trimester to the developing brain, the maternal thyroid hormones play an essential role in fetal neurodevelopment.[137] A relative state of hypothyroidism in a developing fetus may contribute to the neurotoxic effects of PCBs.[28] PCBs may alter thyroid functioning and signaling through a variety of mechanisms such as transport disruption, enhanced hepatic catabolism, inhibition of thyroid hormone, and direct or indirect agonist or antagonist action on the thyroid receptor.[138]

PCBs may also impact male fertility via androgen disruption resulting in changes in sperm morphology, count, penetration efficacy, and motility.[139-141] A study of 212 children at age 11 years whose mothers consumed PCB-contaminated fish during pregnancy found deficits in full scale and verbal IQ after controlling for potential confounding variables such as socioeconomic status; the strongest effects were related to memory and attention.[142] The authors concluded that in utero exposure to PCBs in concentrations slightly higher than those in the general population can have a long-term impact on intellectual function.[142]

Polybrominated Diphenyl Ethers (PBDEs)

PBDE exposure during developmental periods have been associated with adverse thyroid, reproductive, and behavioral effects in animals.[143] Studies in humans found developmental exposure to several PBDE congeners were associated with lower scores on tests of mental and physical development at 12 to 48 and 72 months (prenatal exposure),[144] and delay in time to pregnancy (periconception exposure).[145] The findings of a 2010 study, which measured the concentration of 10 PBDE congeners, free thyroxine (T4), total T4, and thyroid-stimulating hormone (TSH) in 270 pregnant women around the 27th week of gestation suggest that exposure to PBDEs is associated with lower TSH during pregnancy, findings which may have implications for maternal health and fetal development.[146]

Perfluorochemicals

It is well documented that PFOS and PFOA are ubiquitous and extremely persistent in humans and the environment.[147] Extensive animal data document the main health effects of PFOS and PFOA are hepatotoxicity, developmental toxicity, immunotoxicity, hormonal effects, and carcinogenicity.[147] The findings of a 2009 study suggest that PFOS and PFOA exposure at plasma levels seen in the general population may reduce fecundity.[148] A 2013 study of a population exposed to PFOA in drinking water contaminated by releases from a nearby chemical plant found PFOA exposure associated with kidney and testicular cancer.[149]

Other Contributing Factors

The health risks of exposure to environmental contaminants can also be enhanced or diminished by external and internal factors (Fig. 22.4).[150] Some external factors can increase stress on the system, such as lack of access to health care, social and racial discrimination, or poverty. For example, socioeconomic and racial disparities exist with regard to environmental toxicant exposures.[151] Disparities in environmental contaminant exposure have been demonstrated with many environmental contaminants (e.g., air pollution); Hispanic, African American, and Asian/Pacific Islander mothers experienced higher mean levels of air pollution and were more than twice as likely to live in the most polluted counties compared with White mothers after controlling for maternal risk factors, region, and educational status.[152]

Other external factors can create resiliency to competing influences on health, such as good social support networks, access to services, and stable incomes. Internal factors such as age, gender, and genotype can also influence susceptibility to diseases and disorders.

The interplay of the biological, behavioral, psychological, social, and environmental factors that influence health occurs throughout all stages of life. Recognition of these influences over time underlies the "life course" perspective, which conceptualizes perinatal outcomes as a product of not only the 9 months of pregnancy but also the entire life course of the mother from conception (or before) onward leading up to pregnancy.[153]

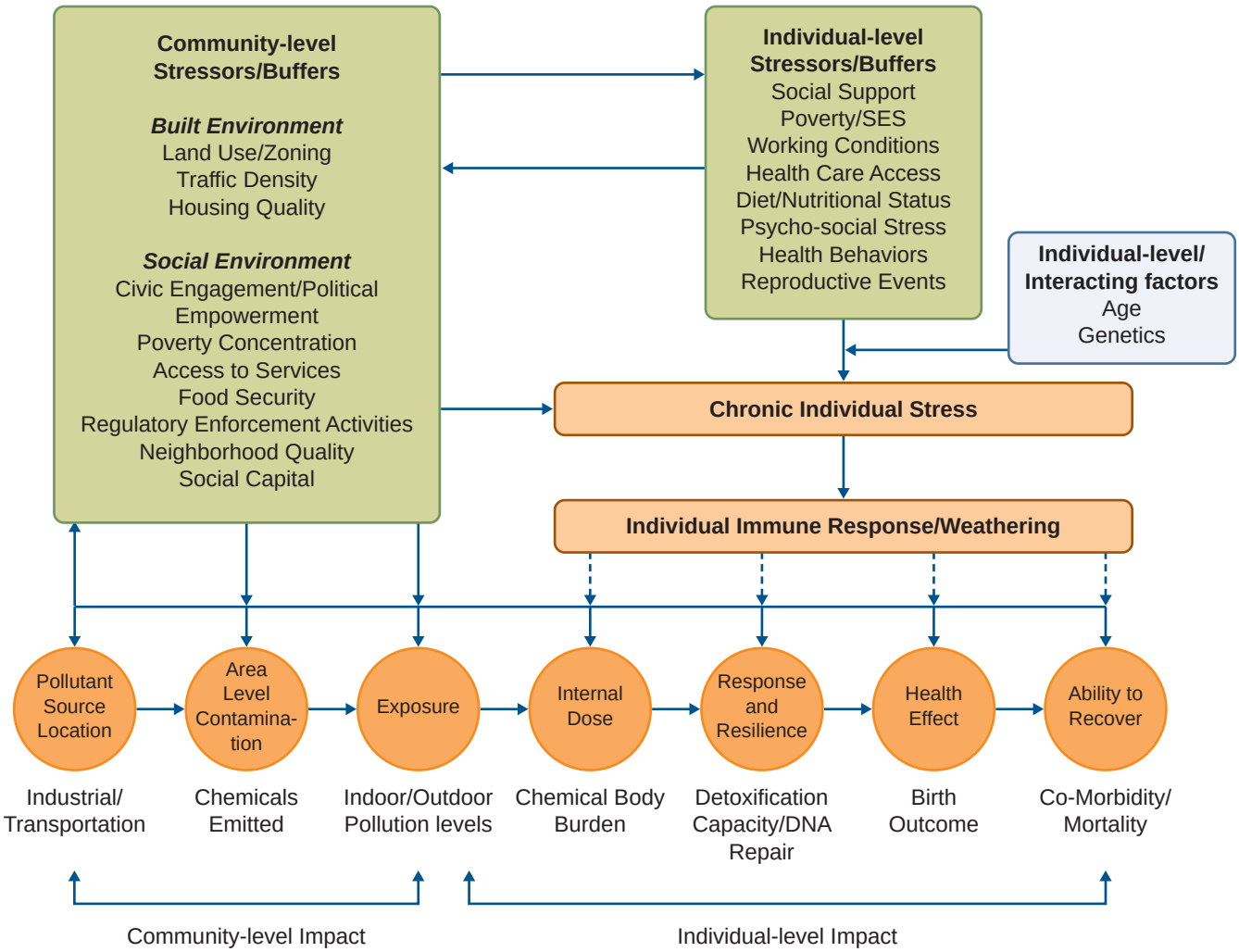

FIGURE 22.4 Factors that can influence the susceptibility to disease. Clinical management of environmental and occupational exposures. (Adapted from Morello-Frosch R, Shenassa ED. The environmental "riskscape" and social inequality: implications for explaining maternal and child health disparities. *Environ Health Perspect*. 2006;114[8]:1150–1153.)

Moreover, human beings are exposed to numerous chemicals during development and throughout life and thus mixed exposures need to be considered in a life-course approach to disease.

PREVENTION

Overview

Clinical practice offers a key point of intervention to prevent harm from hazardous environmental exposures. In 2013, the American College of Obstetricians and Gynecologists (ACOG) Committee for Underserved Women and the American Society for Reproductive Medicine (ASRM) Practice Committee issued a groundbreaking Committee Opinion: Exposure to Toxic Environmental Agents and Companion Paper.[16] The ACOG/ASRM Opinion found that "the evidence that links exposure to toxic environmental agents and adverse reproductive and developmental health outcomes is sufficiently robust, and the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine join leading scientists and other clinical practitioners in calling for timely action to identify and reduce exposure to toxic environmental agents while addressing the consequences of such exposure." Similarly, the American Academy of Pediatrics has had an environmental health committee for over half a century and since 1999 has published a clinicians' handbook for the prevention of childhood diseases linked to environmental exposures.[154]

As recognized by the ACOG/ASRM Opinion, obstetricians, gynecologists, and other reproductive health care providers can be extremely effective in reducing exposure to toxic contaminants in their patients' environments.[16] Many individuals hoping to bear children are intensely interested in the impact of environmental exposures on their pregnancies and the health of their future children. Their health care provider can serve as a science-based source of guidance on how to avoid

potentially adverse exposures. More importantly, many people who may eventually have or want to have children lack awareness of potential risks to their fertility and their future children's health. Therefore, in addition to the current queries about a patient's alcohol and smoking history, clinicians need to be prepared to provide anticipatory guidance and respond to patient inquiries about hazardous environmental exposures encountered at home, at work, and in the community.[155] Beyond the clinic, the active participation of well-informed health professionals is critical to translating scientific findings as they unfold into policies to improve birth outcomes at a larger scale (Table 22.4).

MANAGEMENT OF THE GENERAL POPULATIONS

Identify Patients With Hazardous Exposures

Take an occupational and environmental health history for all patients. Patient risk is a function of the toxicity of the compound and exposure. Routes of exposure are dermal, ingestion, and/or inhalation. Key determinants of exposure and its effects are concentration, frequency and duration, and patient vulnerability, including any underlying health conditions.[156] Socioeconomic and racial disparities exist with regard to environmental

TABLE 22.4 Management of Exposure to Environmental Contaminants Beyond the Clinic Walls

There is uncertainty in the science, as science is always incomplete. What is a practicing physician to do? As noted by Sir Bradford Hill, the epidemiologist who determined that cigarette smoking was a risk factor for lung cancer,

All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time. Sir Bradford Hill 1965 address to the Royal Society of Medicine.

Consistent with Sir Bradford Hill's call to action, historically, clinicians and other health care practitioners have acted on the scientific knowledge at hand to help spur preventive public policy action on environmental and other public health issues. For example, physician involvement played an important role in shifting the public debate on smoking, and had they been active earlier in tobacco control campaigns, many people could have been spared immense suffering. Professional organizations of physicians have consistently called for regulatory and other efforts to address the environmental threats to human health based on the weight of the available science. For example, the American Medical Association (AMA) has adopted science-based policies promoting the incorporation of environmental health into medical education, supporting reforms in chemical policy, and addressing mercury exposure and other key environmental health issues. Most recently, AMA has made a major commitment to participate in actions to address climate change and adopted a policy to promote the engagement of clinicians and policy makers in creating a healthy and sustainable food system.[39]

In 1968, 2 years before the 1970 Clean Air Act established the National Ambient Air Quality Standards for particulates, the California Medical Association (CMA) established policy to "vigorously support all rational efforts for the control of air pollution," as well as to "urge the support of studies and the enactment of laws that will assure a healthful air supply in the future." In the ensuing 40 years, the CMA has followed this pioneering step by enacting numerous additional policies calling for increasingly comprehensive steps to protect the public from the health effects of air pollution.[39]

In 2007, a multidisciplinary group of international physicians and researchers was convened in the Faroe Islands to highlight new insights into the effects of prenatal and early postnatal exposure to chemical agents, and their sustained effects on the individual throughout the lifespan.[12] The scientific consensus that emerged from the conference greatly expands the centuries-old precepts of toxicology and holds tremendous import for reproductive health, concluding that,

Research into the environmental influence on developmental programming of health and disease has . . . led to a new paradigm of toxicologic understanding. The old paradigm, developed over four centuries ago by Paracelsus, was that "the dose makes the poison." However, for exposures sustained during early development, another critical, but largely ignored, issue is that "the timing makes the poison." This extended paradigm deserves wide attention to protect the foetus and child against preventable hazards.[12]

In 2008, the University of California, San Francisco, and the Collaborative on Health and the Environment cosponsored the *Summit on Environmental Challenges to Reproductive Health and Fertility*, a groundbreaking gathering that brought together over 400 scientists, clinicians, patient and health-affected and community organizations, and policy-makers, many of whom are leaders in their respective fields and organizations. The Summit highlighted and consolidated the current science on environmental reproductive health, connected diverse constituents of the field, and developed a set of strategic recommendations for progress in research, policy, health care and occupational health, setting the stage for subsequent achievements in this area.[13]

In 2009, the Endocrine Society—the premier professional organization for basic and clinical endocrine research and the treatment of endocrine disorders—created a Task Force charged with summarizing current knowledge about endocrine disrupting chemicals, including possible mechanisms of action and potential health risks, and recommended actions the Society could take to promote research on endocrine disrupting chemicals. The Endocrine Society review recommended,

Until such time as conclusive scientific evidence exists to either prove or disprove harmful effects of substances, a precautionary approach should be taken in the formulation of EDC [endocrine-disrupting chemicals] policy.[37]

In 2010, the National Cancer Institute's President's Report on Cancer concluded that "*the true burden of environmentally induced cancer has been grossly underestimated. The prevailing regulatory approach in the United States is reactionary rather than precautionary. That is, instead of taking preventive action when uncertainty exists about the potential harm a chemical or other environmental contaminant may cause, a hazard must be incontrovertibly demonstrated before action to ameliorate it is initiated. . . . the public bears the burden of proving that a given environmental exposure is harmful.*" [25] The President's Panel recommended,

A precautionary, prevention-oriented approach should replace current reactionary approaches to environmental contaminants in which human harm must be proven before action is taken to reduce or eliminate exposure. Though not applicable in every instance, this approach should be the cornerstone of a new national cancer prevention strategy that emphasizes primary prevention, redirects accordingly both research and policy agendas, and sets tangible goals for reducing or eliminating toxic environmental exposures implicated in cancer causation.[25]

In 2013, the American College of Obstetricians and Gynecologists Committee for Underserved Women and the American Society for Reproductive Medicine Practice Committee issued a groundbreaking Committee Opinion: Exposure to Toxic Environmental Agents and Companion Paper.[16] The ACOG/ASRM Opinion recognizes that *"patient exposure to toxic environmental chemicals and other stressors is ubiquitous, and preconception and prenatal exposure to toxic environmental agents can have a profound and lasting effect on reproductive health across the life course."* The Opinion concludes that ACOG and ASRM *"join leading scientists and other clinical practitioners in calling for timely action to identify and reduce exposure to toxic environmental agents while addressing the consequences of such exposure."*[16]

contaminant exposures; understanding the environment of patient population can help target high-risk exposures.[151] Women of childbearing age with occupational exposures to substances with reproductive and developmental toxicity are at high risk and susceptible to adverse reproductive outcomes.[157] Management of occupationally exposed patients is detailed in the following section.

Advise All Patients on Prevention Measures

Patient visits offer an opportunity for health care providers to advise patients about steps they can take to avoid toxic exposures. Clinicians should intervene early to prevent exposure by alerting their patients to the hazard and providing guidance on how to avoid toxic exposures. By the first prenatal care visit, disruptions of organogenesis may have already occurred. Anticipatory guidance can include information about how to avoid exposure at home, in the community, and at work. Clinicians can have science-based responses for common questions readily available as a handout for patients in the office or for discussion when questions arise. Examples of downloadable science-based patient educational materials and web links to a wide range of topics can be found at the University of California, San Francisco's Program on Reproductive Health and the Environment website http://prhe.ucsf.edu/prhe/toxicmatters.html. A case study on advising a patient about how to address an environmental exposure is presented in Table 22.5.

Refer Patients When Necessary

Patients identified with occupational exposures of concern can be referred to experts in occupational and environmental medicine and/or toxicology for follow-up. The Association of Occupational and Environmental Clinics (AOEC) maintains a Web-based clinical directory of specialists in occupational and environmental health medicine in the United States, Canada, and Germany. All AOEC member clinics are multidisciplinary in staff and meet specific criteria that promote providing high-quality health care and patient rights (http://www.aoec.org/).

Report

Reporting identified hazards by clinicians is critical to prevention. A patient with a hazardous exposure or an adverse health outcome can be a sentinel for an unrecognized and/or larger public health hazard. Astute practitioners have played vital role in the identification of environmental hazards.[158] For example, the reproductive toxicity of a common solvent used in many consumer products was first described in a case report of a stillbirth.[159] Physicians in the United States are required to report illnesses or injuries that may be work related; however, reporting requirements vary by state.

Occupational exposures have the potential to be of great relevance to the health of the OB/GYN patient population. Almost two-thirds (62%) of working women and men are of reproductive age and the majority of

TABLE 22.5 Case Study: Responding to Questions About Future Risk That May Arise After an Exposure

A young woman comes to her annual physical with questions about her mercury level. She recently participated in a study that measured hair mercury levels and sent the results to the participants. She is hoping to become pregnant in the next 6 months and is worried that her mercury level is too high and will harm the baby. She wonders what she can do to lower her mercury body burden.

Patients may present with specific concerns about a known exposure in their workplace or home or have testing results for contaminants in their body. They may be worried that an exposure will harm them or their children and may specifically wonder if they are at an increased risk for adverse pregnancy outcomes or developing a particular disease such as cancer. For the health care provider, addressing these concerns often requires obtaining more history from the patient about the exposure, including the specific chemical(s) of concern, the dose, timing, route of exposure, number of exposures, and whether there were any associated symptoms that might herald a substantial exposure.

It is often impossible to quantify or predict how much greater risk a person faces from an environmental exposure. In most situations, the exposure happens only once or a few times, is at a low concentration, and it is not likely to substantially increase the risk of adverse effects above that seen in the general population. In addition, there is often little or nothing that can be done in retrospect about the exposure incident. Providers can use this opportunity to offer reassurance and to educate the patient on how to reduce future exposures. On the other hand, some exposures occur at higher doses or on an ongoing basis, for example, in an industrial or agricultural environment where higher concentrations of chemicals or pesticides may be used. In these situations, the provider will need to obtain a more thorough exposure history and more information about the toxicity of the chemical to address the specific patient concerns. In the case of a reproductive toxicant, any indication that an exposure may be significant or recurrent may warrant closer monitoring, additional testing, or precautionary action to remove the patient from the exposure. Some people may ask about undergoing special treatments to reduce the level of contaminants in their body. Some common treatments include chelation therapy, special diets, or medicines. In general, most of these treatments are not effective, can have serious side effects, and should be regarded with caution. Chelation therapy can be used appropriately for treating acute, severe metal poisoning. However, it is not generally accepted for use to decrease body burdens due to past exposures, especially in adults with no symptoms of toxicity. All chelating agents have side effects; most commonly, these include abdominal discomfort, nausea, liver damage, neutropenia, decreased blood pressure, and allergic reactions. In addition, chelators may bind other divalent mineral cations essential for normal physiologic function. In the case of mercury, the half-life of the metal in the human body is about 60 days. Appropriate management of an asymptomatic patient with a confirmed elevated mercury level would include advice about avoiding mercury from fish and a review of other possible sources of mercury exposure. Repeat testing to assure that the level is declining is also useful. A woman of reproductive age may be counseled to delay pregnancy for 6–8 months as a precautionary measure. When there is concern about an exposure that may result in adverse effects, consultation with a specialist in occupational/environmental medicine or toxicology may be warranted. In all situations, patient education on how to prevent and reduce future exposures is essential.

From Solomon G, Janssen S. Talking with patients and the public about endocrine-disrupting chemicals. In: Gore A, ed. *Endocrine-Disrupting Chemicals: From Basic Research to Clinical Practice*. Totowa, NJ: Humana Press; 2007.

children (55%) are born to working mothers (2003 U.S. Census Bureau data[160]).

Clinicians can provide critical support to patient decision making by providing valuable advice about whether workplace exposures can harm a pregnancy or present other health hazards and by making timely referrals to experts in occupational medicine when hazardous exposure situations are identified. It is optimal to determine potential hazards and risks from workplace exposures before pregnancy occurs. Preconception recognition of hazards allows preventive steps to be taken before organogenesis and other early and vulnerable stages of pregnancy occur.

To counsel patients about their workplace exposures, clinicians should[161,162]:

- Obtain a thorough job history; examples of occupational exposures of concern include metals (industrial and dental), solvents (labs, dry cleaning, semiconductor, electronics, petrochemical), formaldehyde (wood processing), ethylene oxide, anesthetic gases, and antineoplastic drugs (dental and medical) as well as pesticides (agricultural workers).[163]
- Gain an understanding of the workplace setting.
- Review material safety data sheets (MSDS) for the products or chemicals handled by or near their patient. MSDS can be obtained from the manufacturer or employer and some are online, for example, the Vermont Safety Information Resources site at www.siri.org. It is important to keep in mind that there are systemic shortcomings of MSDS and a high percentage of them are plagued by incomplete or inaccurate information.[164,165]
- Gather as much information as possible about exposure pathways, duration, and magnitude.

A household products database is available on the Internet and includes health effect information for more than 4000 products (www.householdproducts.nlm.nih.gov).

Patients have a legal right to a safe and healthy workplace, including protection from exposure to chemicals with reproductive and developmental toxicities. However, patients confront many economic, social, and other barriers to securing their rights, and compliance with employers' legal responsibilities does not guarantee the workplace is free of reproductive, developmental, or other health hazards. This is because:

- Most workplace chemicals have not been tested to determine whether they can harm human reproduction and development. In general, sufficient, publicly available information about the toxicologic properties of the vast majority of chemicals in commercial circulation is largely lacking.
- Most legal workplace exposure limits for chemicals are not based on protecting against reproductive and developmental harm, even for chemicals that are known to cause these effects. For example, a 2007 study by the California Environmental Protection Agency (Cal-EPA) found that 5 of 19 workplace chemicals known to cause reproductive or developmental harm do not have a permissible exposure limit, and 14 are not regulated as reproductive or developmental hazards.[166] The Cal-EPA study also found that 44 of 106 workplace chemicals known to the state of California to cause cancer (not including drugs, banned chemicals, and pesticides) do not have a permissible exposure limit, and 62 are not regulated as carcinogens.
- Regulations that govern occupational exposure to toxic substances permit risk levels far in excess of what is deemed "acceptable" risk for nonoccupational exposure scenarios. Illustrative of this disparity, the 2007 Cal-EPA study identified six workplace chemicals with permissible risks of greater than one case of cancer for every 10 exposed workers.[166]

Resources and referrals that can aid the practicing clinician in addressing some of these challenges by assisting in identifying hazardous situations and assessing and communicating patient risk are listed at the end of this chapter.

CLINICAL NOTES

- Women of childbearing age have ubiquitous exposure to synthetic chemicals and metals linked to reproductive, fertility, and/or developmental health effects. Exposures occur at patients' homes, workplaces, and communities, and via food, water, air, and consumer products.
- The embryo, fetus, and developing human are highly vulnerable to exposure to even small amounts of environmental toxicants. Exposures during critical windows of development may result in adverse, permanent effects that can have lifelong and even intergenerational impacts on health. Thus, reducing or eliminating exposure to environmental contaminants *prior* to conception is the most effective strategy for preventing adverse health consequences.
- A wide range of adverse reproductive and developmental health outcomes are linked to environmental contaminants encountered in the daily lives of OB/GYN patients, including impacts on pregnancy outcomes, reproductive health and fertility, including timing and progression of pubertal development, and cancers of the reproductive tract. Examples of commonly encountered environmental contaminants with reproductive and/or developmental impacts are lead, mercury, pesticides, solvents, BPA, dioxin, phthalates, PCBs, PBDEs, and PFCs.

(continues)

- When making decisions about patient exposure to environmental and occupational exposure to chemicals, clinicians must rely on in vitro and in vivo studies for early warnings of adverse effects and human observational studies to assess the nature and extent of the damage.
- Management of the general patient population: Identify patients with hazardous exposures, advise all patients on prevention measures, refer patients when necessary, and report identified hazards.
- Management of the occupationally exposed patient population: Obtain a thorough job history; gain an understanding of the workplace setting; review MSDS for the products or chemicals handled by or near their patient; gather as much information as possible about exposure pathways, duration, and magnitude; and assess whether the patient has special medical conditions that make him or her unusually susceptible to harm from any workplace hazard. Compliance with employers' legal responsibilities does not guarantee the workplace is free of reproductive, developmental, or other health hazards.
- Beyond the clinic, the active participation of well-informed health professionals in professional and public policy arenas is critical to translating scientific findings as they unfold into policies to improve birth outcomes at a larger scale.

ADDITIONAL RESOURCES AND REFERRALS

Medical Referrals/Expertise

- The Association of Occupational and Environmental Clinics is dedicated to the practice of occupational and environmental medicine (www.aoec.org).
- Pediatric Environmental Health Specialty Units (PEHSU) provide education and consultation on children's environmental health (www.aoec.org/pehsu.htm).
- Organization of Teratology Information Specialists (OTIS) provides information to health care professional and patients about exposure during pregnancy and lactation (http://www.mothertobaby.org/).
- Multiple examples regarding obtaining an exposure history exist and can be found at: http://prhe.ucsf.edu/prhe/clinical_resources.html.

Authoritative Lists/Sources of Information About Chemicals With Reproductive and Developmental Toxicity

- U.S. National Toxicology Program, Center for Evaluation of Risks to Human Reproduction (NTP/CERHR) provides up-to-date information about potentially hazardous effects of chemicals on human reproduction and development (http://ntp.niehs.nih.gov/go/ohat).
- U.S. Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS) evaluates risk information on human health effects that may result from exposure to environmental contaminants (www.epa.gov/iris/).
- California Environmental Protection Agency (Cal-EPA) provides the list of chemicals known by the State of California to cause cancer or reproductive or developmental toxicity (http://oehha.ca.gov/prop65/prop65_list/Newlist.html).

Other Governmental and Academic Sources of Information

- University of California San Francisco, Program on Reproductive Health and the Environment focuses on the intersection of science, medicine, policy, and community engagement in each of our areas of activity: targeted research, expanding clinical practice, and advancing science-based policy solutions (http://prhe.ucsf.edu/).
- U.S. Centers for Disease Control and Prevention is the US federal agency that conducts critical scientific research and data collection in order to provide health information that protects the health of the population; it responds when health risks or issues arise. It has an environmental health organization and several other related organizations that address environmental and occupational health issues and the interface between these and reproductive health issues (www.cdc.gov).
- Agency for Toxic Substances and Disease Registry (ATSDR) evaluates the human health effects of hazardous substance exposures and produces "toxicologic profiles" for hazardous substances found at National Priorities List (www.atsdr.cdc.gov).
- The National Institute for Occupational Safety and Health (NIOSH) provides information on chemical safety, workplace health hazard evaluations, and reproductive health and occupational exposures (www.cdc.gov/niosh).
- ToxNet provides a system of databases on toxicology, hazardous chemicals, and environmental health (http://toxnet.nlm.nih.gov/).
- Household Hazardous Substance Database links over 6000 consumer brands to health effects from MSDS and allows scientists and consumers to research products based on chemical ingredients (www.householdproducts.nlm.nih.gov/products.htm).
- U.S. Equal Employment Opportunity Commission (EEOC) provides information on laws and regulations related to pregnancy, employment, and disability (www.eeoc.gov/laws/types/pregnancy.cfm).
- The National Pesticide Information Center (NPIC) maintains a database about pesticide safety and toxicity. The organization also runs a toll-free hotline for pesticide questions (1-800-858-7378) (www.npic.orst.edu).
- e.hormone is administered by the Center for Bio-environmental Research at Tulane/Xavier Universities

and provides background and up-to-date information about endocrine disruption and other environmental signaling (http://e.hormone.tulane.edu/).

- INCHEM (International Program on Chemical Safety) provides internationally peer-reviewed information on chemicals commonly used throughout the world from intergovernmental organizations (http://www.inchem.org/).
- EMCOM is a Canadian-based information resource about endocrine disrupting substances (www.emcom.ca).

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SECTION III

Special Populations

CHAPTER 23

Pediatric and Adolescent Gynecology

Mariel A. Focseneanu and Diane F. Merritt

Pediatric and adolescent gynecology is a distinct subspecialty involving the unique gynecologic problems of the neonate, prepubertal child, and developing adolescent. A practicing obstetrician–gynecologist should be able to recognize, treat, or triage the most common office-based problems that arise in this discipline and know when to refer to a specialist.

NORMAL FINDINGS

Training in obstetrics and gynecology focuses on the care and management of the expectant and puerperal mother and much less routinely on the examination of a newborn after delivery. However, it is good practice for the delivering clinician to perform a brief genital examination of every newborn to determine if the external genital structures, urethra, and anus appear to be normal. The breast tissue of newborns of both genders may have breast buds or secretions due to maternal estrogen. In the newborn female, presence of a patent vagina must also be assessed. The female infant initially has prominent labia and a thickened hymen. Vulvar edema and a mucous vaginal discharge are common. If a hymenal polyp or vaginal "tag" is noted on the newborn examination, conservative management is recommended as spontaneous involution often occurs as endogenous estrogen levels fall. Approximately 10% of newborns will have some withdrawal bleeding. In premature infants, relative clitoromegaly may appear as the result of decreased subcutaneous fat. These expected physiologic effects of maternal hormones usually resolve within the first 3 months of life and are not a cause for concern.[1]

Once newborn levels of estrogen decline, the hymenal membrane thins and may become translucent allowing fine vascular details to be seen, and the introital mucosa appears shiny and reddened. The labia minora are small structures usually measuring less than half the length of the introitus, reflecting the lack of endogenous estrogen production. Prepubertal children, lacking lactobacilli, will normally have minimal clear, alkaline vaginal discharge. There are several normal variants of hymen configuration, for example, annular (circumferential), crescentic, and fimbriated (folded). The crescentic hymen was most commonly found among girls surveyed at age 3 years, with an annular hymen being the second most common configuration.[2]

In a prepubertal female, the size ratio of the uterine corpus compared with the cervix is 1:3; in the pubertal child, it is 1:1; and in the adult woman, it is 3:1. The prepubertal ovary is generally about 1 cm^3 in size, and small follicles are seen by high-resolution ultrasound.[3]

Assessment of External Genitalia and Exam Techniques

The American College of Obstetricians and Gynecologists recommends the first visit to the obstetrician–gynecologist for screening and the provision of reproductive preventive health care services and guidance take place between the ages of 13 and 15 years.[4] The American Academy of Pediatrics promotes the inclusion of the gynecologic examination in the primary care setting within the medical home.[5] For this reason, providers who see or treat children or adolescents should become familiar with providing gynecologic examinations for infants, children, and adolescents.

Newborn and Prepubertal Child

When examining a young child, it is important to put the child and parents at ease and gain their trust. The physician should explain to the child and her parent(s) exactly what will be done during the exam and why it is necessary. Focus should be placed on reassuring the parent(s) and explaining that the examination of a child is different from an examination of an adult. The child should be made to feel at ease and allowed to maintain some control of her environment; the goal is to examine the child without causing any traumatization to her. It may be helpful to allow the child to hold a handheld mirror so she may see her genitals at the same time they are being examined.

Children and younger adolescents are concrete thinkers—as such the most meaningful information may be imparted concurrent with the examination. It is important to point out to children after the exam that it was done because the parent or guardian agreed to it. This provides an opportunity to remind children that no one else should touch her genitals and if it happens, she should tell the parent(s) or guardian(s).

The genital examination should be incorporated into a complete physical examination. Begin the examination by visual inspection of the skin for rashes and lesions, and then listen to the heart and lungs. Visualization or palpation of the breast tissue allows determination of Tanner staging. The abdomen should be palpated for masses. The pelvic exam may be deferred until a subsequent visit in order to allow the girl time to develop a relationship with her new physician or provider unless there is a specific problem or urgent situation.

The undergarments may be removed immediately before the examination and the child should be offered and shown how to use a drape. Although the ideal position for good visualization of a young girls genitalia is supine, with her buttocks at the end of a gynecologic examination table, this is not typically feasible in younger children. Alternatively, the parent of a child can be positioned on the examination table, supported by elevating the head of the table, with the child positioned frog-leg style on the parent's lap (Fig. 23.1). Many children feel comforted in the arms and lap of their parent and it is an easy alternative method to allow inspection of the perineum. In the frog-leg position, the labia may be gently separated or gentle lateral traction on the labia majora may be used and this allows for better visualization of the hymen and vaginal orifice (Fig. 23.2A,B). The child may also be allowed to use her own hands to spread the labia laterally to allow visualization of the vaginal introits. After examination in the frog-leg style, the child should be asked to get into the knee-to-chest position on the examination table (Fig. 23.3). The knee-to-chest position offers an improved view of the vagina and more thorough inspection of both the posterior and anterior hymenal area.

Older patients may be able to be placed in the supine position but this position does not allow direct eye contact between the patient and her examiner. For this reason, we suggest that older children and teens sit up with their back supported at a 45-degree angle and their feet in stirrups. With the perineum exposed, a teaching examination can proceed (see next section).

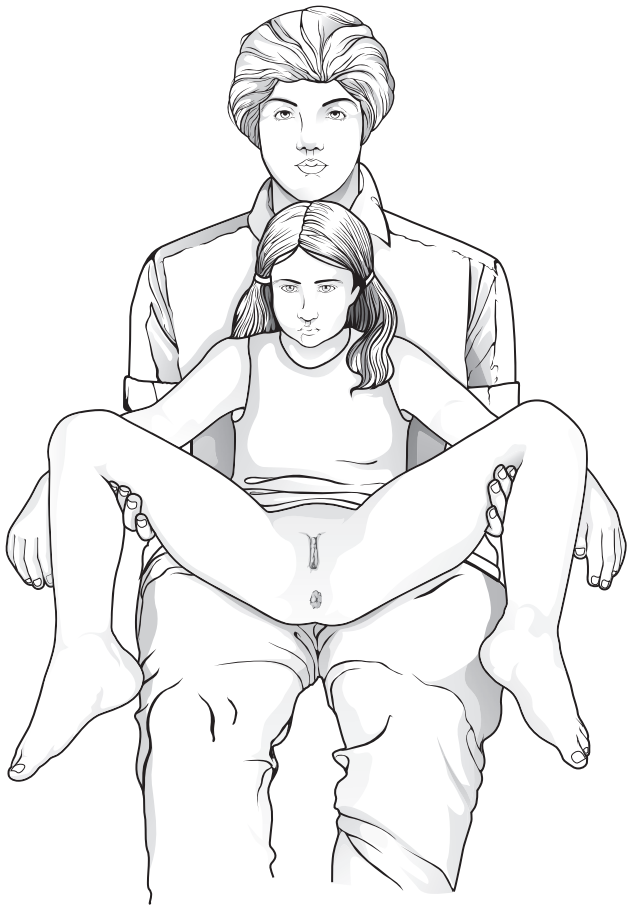

FIGURE 23.1 Picture of child in frog leg in parent's lap. (Used with permission from Finkel MA, Giardino AP, eds. *Medical Evaluation of Child Sexual Abuse: A Practical Guide*. 2nd ed. Thousand Oaks, CA: Sage Publications; 2002. © Sage Publications, Inc.)

Examination of a prepubertal child should not be done without some means of magnifying the area. A handheld magnifying glass with or without light, colposcope, or even an otoscope with the truncated ear canal piece removed may be used. The exam should be described in detail in the chart with a comment regarding the size, shape, or any abnormalities of the labia majora and minora (in children it may be hard to distinguish between these), clitoris, clitoral hood, urethra, vaginal orifice and vestibule, hymen, perineal body, and anus inclusive.

Because of their hypoestrogenic state, the genital tissues of young girls are very sensitive to touch and may be easily lacerated by instruments and even cotton tip swabs. A vaginal speculum should not be used in the pediatric patient. If a vaginal infection needs to be ruled out, a culture should be obtained by placing a very small moistened cotton swab, for example, a Calgi swab or a

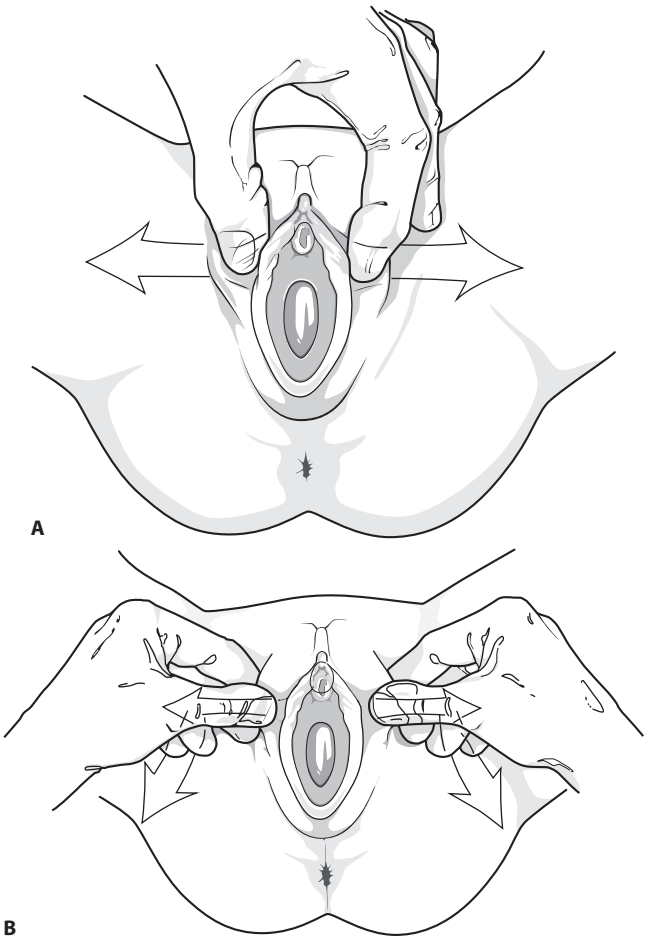

FIGURE 23.2 **A, B:** Separation and lateral traction. (Used with permission from Finkel MA, Giardino AP, eds. *Medical Evaluation of Child Sexual Abuse: A Practical Guide*. 2nd ed. Thousand Oaks, CA: Sage Publications; 2002. © Sage Publications, Inc.)

small Dacron swab (male urethral size), just through the hymen with every effort made not to touch the sensitive hymen. If this is not possible, the culture swab may be placed between the labia, although this may not yield adequate sampling for diagnosis.

If the vagina needs to be flushed, for example, looking for a foreign body, a soft rubber catheter works quite

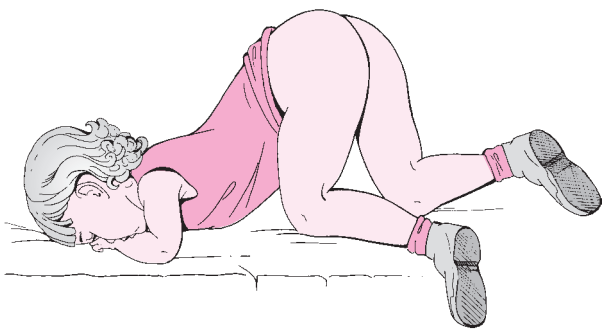

FIGURE 23.3 Child in the knee-to-chest position. (From Gibbs RS, Karlan BY, Haney AF, Nygaard IE, eds. *Danforth's Obstetrics and Gynecology*. 10th ed. Philadelphia: Lippincott Williams and Wilkins; 2008.)

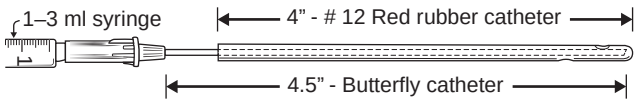

FIGURE 23.4 Catheter within a catheter. (Used with permission from Pokorny SF, Stormer, J. A traumatic removal of secretions from the prepubertal vagina. *Am J Obstet Gynecol*.1987;156:S81–S82. © 1987 Mosby.)

well. However, it is not ideal for obtaining secretions for culture because the tip will be sucked against the vaginal wall when the vaginal fluid (either naturally occurring or the combination of saline that has been introduced into the vagina via the catheter and then is aspirated) is aspirated. One option is to use a "catheter within a catheter" (Fig. 23.4). A 4.5 in butterfly intravenous (IV) tube may be passed into the distal 4.5 inches of a soft, no. 12, red rubber catheter that is attached to a 1 to 3 mL syringe to allow for 0.5 to 1 mL of fluid to be flushed into the vagina and aspirated back into the syringe. This can be done several times to get a good mixture of upper vaginal secretions and the aspirant may be sent for wet mount, Gram stains, cultures, and forensic material. The lab should be told that the specimen was obtained from a prepubertal child. Most children are amenable to this procedure if they are shown there is no needle attached to the apparatus and it may be helpful to place a few drops of the liquid on their hand or fingers to reassure them.

The vaginal pH in prepubertal girls is 6.5 to 7.5 and is therefore not useful for the diagnosis of bacterial vaginosis or trichomonal infections in these girls.

If a more thorough examination of the vagina of a prepubertal child is necessary (e.g., unexplained vaginal bleeding, suspicion of a foreign object or trauma), vaginoscopy is recommended. The vaginal endoscopic examination via cystoscopy or hysteroscopy employs normal saline (in a bag draining to gravity) to distend the vagina while the labia are held gently together, allowing the vagina to distend and facilitate evaluation. Application of 2% lidocaine jelly to the external vaginal area and to the tip of a vaginoscope enables more comfortable placement into the vagina. This may be accomplished in a cooperative patient in an outpatient setting or may require general anesthesia in a young or frightened child.[6] A young child's vagina is about 5 cm in length and the mucosa is red, thin, and slightly folded. The cervix is small, with a central opening, and is often flush with the vagina. Vaginoscopy may cause petechiae of the vaginal mucosa given how thin and sensitive it is.

Clitoral size may be determined by the clitoral index, which is calculated as the product of the length and width of the clitoris and expressed in square millimeters. Charts indicating the normal clitoral index by age are available (Table 23.1). If the clitoris is enlarged, causes of androgen stimulation should be sought (Table 23.2).

It is important to realize that hymens change with age and weight. Infant girls have estrogenized hymens and

TABLE 23.1 Clitoral Index in Girls With Normal and Abnormal Sexual Development

Age (yr)	Normal (n)	Congenital Adrenal Hyperplasia (n)	Central Precocious Puberty (n)	Premature Adrenarche (n)	XO/XY karyotype (n)
0–1	15.1 ± 1.4 (16)	137.9 ± 26.9 (6)			
1–8	15.1 ± 0.9 (29)	225.0 ± 49.0 (5)	20 ± 2 (5)	26 ± 1 (4)	
8–13	16.7 ± 0.9 (18)	212.0 ± 59.0 (4)	17 ± 2 (5)	25 ± 7 (4)	242 ± 171 (2)
13–18	20.7 ± 1.6 (17)	116.0 ± 14.0 (5)			

All values are clitoral indexes in square millimeters.
From Sane K, Pescovitz OH. The clitoral index: a determination of clitoral size in normal girls and in girls with abnormal sexual development. *J Pediatr.* 1992;120(2, pt 1):264–266.

TABLE 23.2 Causes of Clitoromegaly

	Can Present		
Condition	**At Birth**	**After Birth**	**Comments and Reference**
Virilized XX			
Congenital adrenal hyperplasia (CAH)	Yes	Yes	21-Alpha-hydroxylase deficiency and 11-beta-hydroxylase deficiency are the most common. Late presentation does occur.[a,b] (See "Diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency" and see "Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency").
Maternal androgens or synthetic progestational agents	Yes	No	(See "Causes of gestational hyperandrogenism")
Placental aromatase enzyme deficiency	Yes	No	Maternal virilization during pregnancy can be a clue to the diagnosis. (See "Diagnosis and management of gestational hyperandrogenism").
Androgen-secreting tumors	No	Yes	Ovarian[c] and adrenal[d]
Hepatic dysfunction	No	Yes	Report of 10-year-old girl with portal hypertension and impaired hepatic steroid metabolism[e]
Exogenous androgens	Yes	Yes	(Akcam, 2003)[f]
Feminized XY (not true clitoromegaly, but small penis can appear as large clitoris)			
Congenital adrenal hyperplasia (CAH)	Yes	Yes	Examples include 17-hydroxylase deficiency, 3-beta-hydroxysteroid deficiency. (See "Uncommon causes of congenital adrenal hyperplasia").
Androgen insensitivity syndrome (aka testicular feminization syndrome)	Yes	Yes	Complete insensitivity usually presents at birth, whereas partial insensitivity can present at birth or later.[g,h] (See "Diagnosis and treatment of disorders of the androgen receptor").
5-Alpha-reductase deficiency (5aRD)	Yes	No	5aR converts testosterone to DHT. (See "Steroid 5-alpha-reductase 2 deficiency").
Other			
True hermaphroditism	Yes	Yes	Patients can be XX or XY. Genitalia can vary from ambiguous to isolated clitoromegaly.[i]
Mixed gonadal dysgenesis	Yes	No	Most patients are mosaics 45,XO/46,XY. (See "Evaluation of the infant with ambiguous genitalia").
Neurofibromatosis	Yes	Yes	Has been reported both with type 1 and type 2[j]
Vascular malformation	TP	Yes	Report of 5-year-old girl[k]
Sebaceous cyst	TP	Yes	Case report in adolescent girl[l]
Idiopathic	Yes	Yes	Report of two adults with acquired isolated clitoromegaly[m]

TP, theoretically possible but no case report found.
[a]Silverman K, Couey SM, Murmam D. Non-classic 21-hydroxylase deficiency in an 18-year-old female athlete. A case report. *J Pediatr Adolesc Gynecol.* 2000;13:96–97.
[b]Pang S. Congenital adrenal hyperplasia. *Baillieres Clin Obstet Gynecol.* 1997;11:281–306.
[c]Sayer RA, Deutsch A, Hoffman MS. Clitoroplasty. *Obstet Gynecol.* 2007;110:523–525.
[d]Wolthers OD, Cameron FJ, Scheimberg I, et al. Androgen secreting adrenocortical tumors. *Arch Dis Child.* 1999;80:46–50.
[e]Speiser PW, Susin M, Sassano H, et al. Ovarian hyperthecosis in the setting of portal hypertension. *J Clin Endocrinol Metab.* 2000;85:873–877.
[f]Akcam M, Topaloglu A. Extremely immature infant who developed clitoromegaly during the second month of her postnatal life probably due to frequent whole blood transfusion from an adult male. *Pediatr Int.* 2003;45:347–348.
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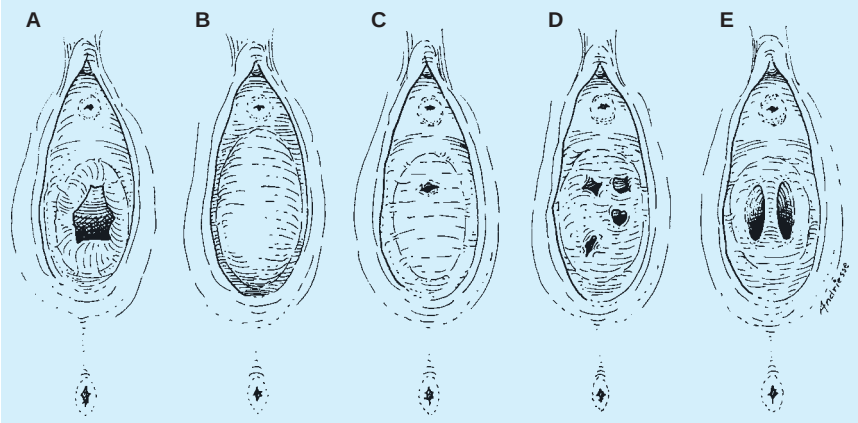

FIGURE 23.5 Anatomic variations of the normal hymen. **A:** Normal. **B:** Imperforate. **C:** Microperforate. **D:** Cribriform. **E:** Septate. (Reproduced with permission from Laufer MR. Structural abnormalities of the female reproductive tract. In: Emans SJ, Laufer MR, Goldstein DP, eds. *Pediatric and Adolescent Gynecology.* 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. Copyright © 2012 Lippincott Williams & Wilkins.)

may have a prominent ridge at 6 o'clock. The hymen of prepubertal girls is unestrogenized, thin, and may have a multitude of appearances (Figs. 23.5 and 23.6).

Infantile perianal pyramidal protrusion (IPPP) is a perianal lesion that has been previously described as a skin tag or fold and is seen almost only in girls[7] (Fig. 23.7). It may be perineal in location rather than perianal but is typically midline and usually anterior to the anus, although they may rarely be posteriorly located to the anus.[8] It is not tender and treatment is not indicated. Clinically, they may undergo cycles of swelling followed by spontaneous resolution.

Pubertal and Postpubertal Adolescent

In the initial examination of the young adolescent, often only the external genital area needs to be viewed, in which case placement of a speculum or an internal examination is not necessary. This often reassures both the patient and her parent who may have negative attitudes about the use of a vaginal speculum and allows the clinician to present the external genital examination in the context of routine adolescent health care.

It is important for clinicians to be familiar with normal variations of pubertal maturation, so that abnormalities of puberty can be recognized and treated in a timely manner. Puberty consists of a series of predictable sequence of events and the most common staging system is the "Tanner stages" of puberty (Figs. 23.8 to 23.10).

Normal puberty begins when gonadotropin-releasing hormone (GnRH) is released from the hypothalamus in a pulsatile manner, activating the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

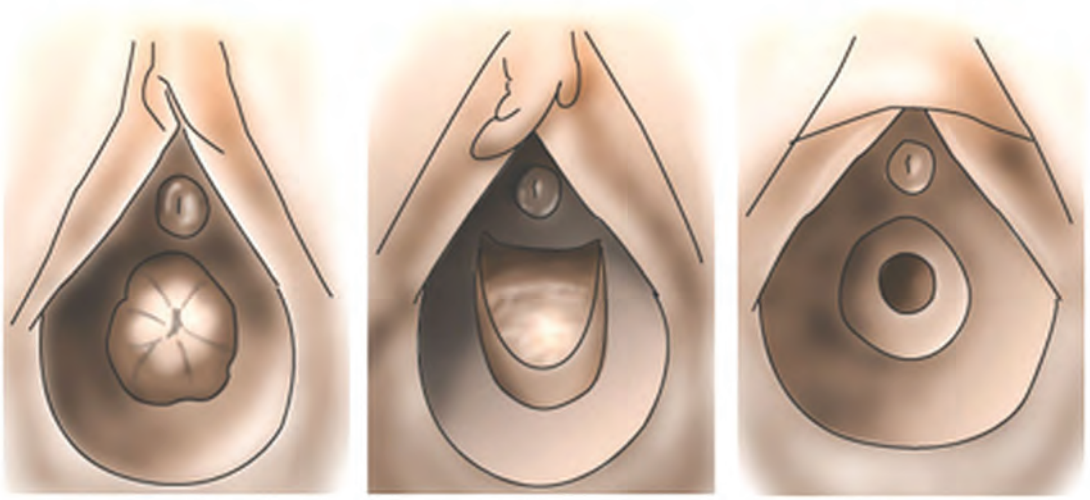

FIGURE 23.6 Normal hymens in prepubertal girls. **A:** Fimbriated or redundant hymen. **B:** Posterior rim or crescentic hymen. **C:** Circumferential or annular hymen. (Modified from Pokorny SF. Configuration of the prepubertal hymen. *Am J Obstet Gynecol.* 1987;157:950.)

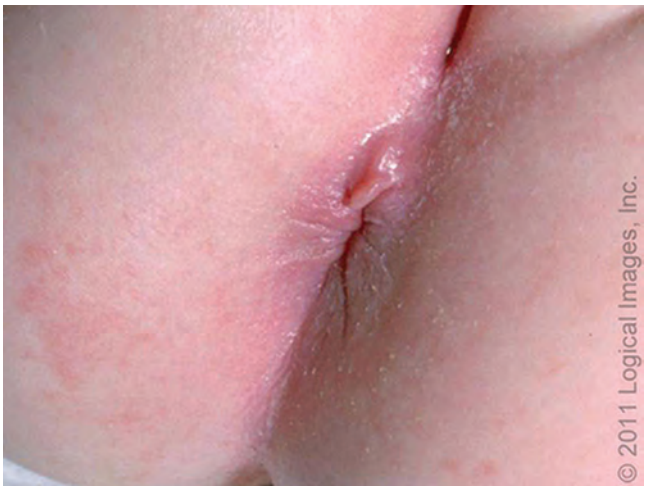

FIGURE 23.7 Infantile perianal pyramidal protrusion. Infantile perianal pyramidal protrusion is a pedunculated perineal lesion, typically located in the midline, just anterior to the anus. It occurs almost exclusively in girls. (Reproduced with permission from www.visualdx.com. Copyright © 2011 Logical Images, Inc.)

from the pituitary. LH induces production of androstenedione from the ovarian theca cells, and FSH induces synthesis of estradiol from the follicular cells. At puberty, changes related to estrogen include breast development, enlargement of the labia minora, and edematous and pink changes in the hymenal tissues. The increase in estradiol causes breast development (thelarche) and the growth spurt in girls.[9] The earliest secondary sexual characteristic in most girls is breast/areolar development, although some may exhibit pubic hair growth first. Menarche occurs, on average, 2.6 years after the onset of puberty.

Adrenarche (pubic hair development) is initiated by adrenal androgen production and usually begins approximately 6 months after thelarche, at an average age of 11 to 12 years. Pubic hair may be a normal first sign of development in some girls (as early as age 7 years), particularly in those of African American descent.[10] The Lawson Wilkins Pediatric Endocrine Society has recommended guidelines for the valuation of premature development, which state that pubic hair or breast development requires evaluation only when it occurs before age 7 years in non–African American girls and before age 6 years in African American girls.[11] These recommendations are controversial, however, as they lower the age threshold for evaluation for precocious puberty and this may lead to failure to identify some children with disease processes that may be amenable to intervention.[12]

Menarche typically occurs within 2 to 3 years after thelarche, at a median age of 12.4 years.[13] Onset of puberty is affected by race, family history, birth weight, nutrition, international adoption, and exposure to estrogenic chemicals. For reasons that remain unclear, the age of menarche has declined to a greater extent in Black girls compared to White girls over the last several decades.[14] When menarche occurs before the age of 12 years, it is associated with increases in weight and body mass index (BMI).[15]

About 17 to 18% of final adult height accrues during puberty, with the limbs exhibiting an accelerated growth prior to the truncal portions of the body.[16] The peak growth velocity usually begins about 2 years earlier in girls than in boys and occurs about 6 months or so prior to menarche.[17] About half of a woman's total body calcium is laid down during puberty.[18,19] Changes in bone growth and mineralization patterns may put some adolescents at increased risk for fracture. If a patient has scoliosis, progression of the degree of scoliosis may occur during puberty as a result of growth in the axial skeleton.

The increase in BMI prior to 16 years of age that is seen with puberty is usually due in increases in fat-free mass; after age 16 years, increasing BMI is primarily due to increases in fat mass.[20]

The vagina and hymen become more distensible during puberty. Despite historical documentation and cultural beliefs, recent research has shown that even an experienced clinician cannot tell if a postpubertal woman has had genital penetration based on the physical examination.[21]

Any signs of inflammation, lesions or pigment changes seen on the exam should be noted. Folliculitis, presenting as tender papules and pustules, has become increasingly common in adolescents who shave their pubic hair.[5] As noted earlier, an enlarged clitoris (>10 mm^3) may indicate elevated androgens. Asymmetry of the labia, where the right and left labia are different in size and appearance, is a normal variant. Some young women are uncomfortable with asymmetric labia or enlarged labia minora and complain about self-consciousness and discomfort while wearing clothing, exercising, or having intercourse. The American College of Obstetricians and Gynecologists (ACOG) does not support performing cosmetic surgical procedures of labia minora unless there is significant impairment in function.[22]

A physiologic clear vaginal secretion may be worrisome for a peripubertal girl or young teen. Teens should be reassured that this nonirritating, nonodorous discharge is normal physiologic leukorrhea and reflects the effect of estrogen on the cells lining the vagina. Peri- and postpubertal children will have normal vaginal secretions with an acidic pH due to the effect of the protective population of lactobacilli that thrive in the glucose-rich environment of an estrogenized vagina.

The examination of adolescents is a golden opportunity to teach genital anatomy and hygiene. Teens appreciate a nonjudgmental and unhurried provider who is willing to answer their questions. As in the pediatric

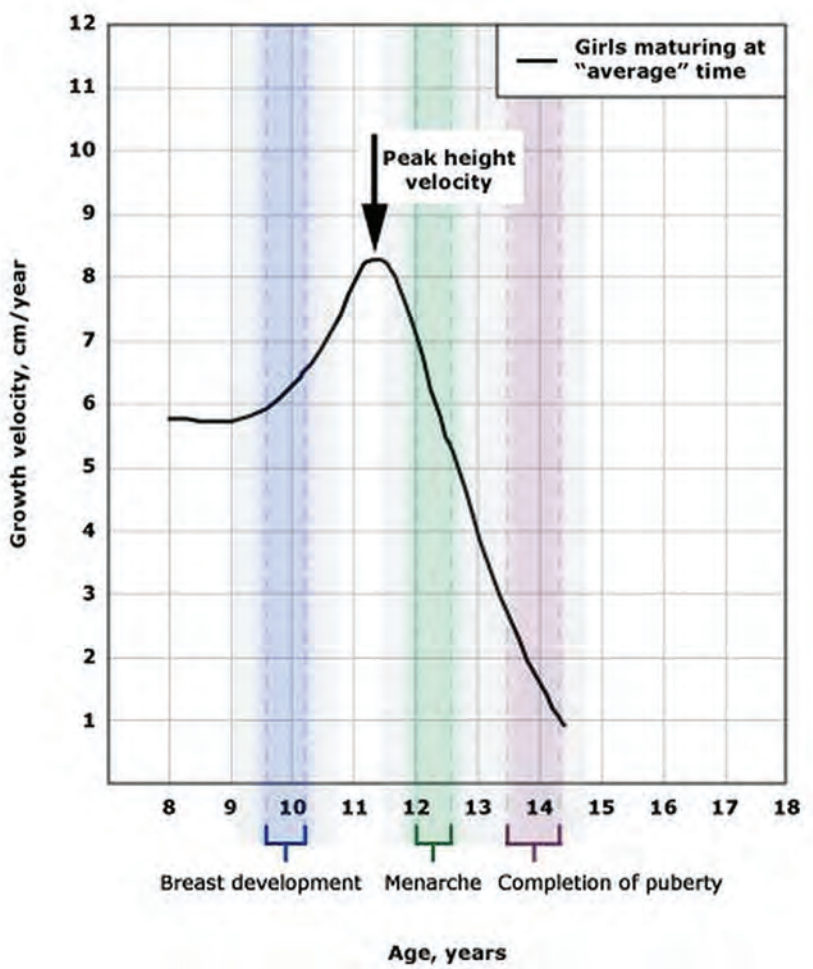

FIGURE 23.8 Sequence of puberty in girls. Sequence of events in girls with average timing of pubertal development in the United States. Black girls tend to reach a milestone at a younger age (left-hand side of the bracket) than White girls (right-hand side of the bracket). The median length of time between the onset of puberty (breast Tanner stage II) and menarche is 2.6 years, and the 95th percentile is 4.5 years. (Data from Biro FM, Huang B, Crawford PB, et al. Pubertal correlates in black and white girls. *J Pediatr.* 2006;148:234–240; Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr.* 1985;107:317–329; Biro FM. Normal puberty. UpToDate Web site. http://www.uptodate.com/contents/normal-puberty. Accessed December 17, 2013.)

patient, examination of the adolescent breast should include Tanner staging. Self-examination of the breast for those aged 13 to 18 years is not recommended because the risk for breast pathology is low.[23] The pelvic exam should be explained prior to beginning the exam. In general, all adolescents benefit from an educational external genital examination, with the provider indicating the anatomic findings while the patient simultaneously watches using a handheld mirror. Instruction in genital hygiene, including wiping from front to back; using wet wipes after bowel movements; cleansing the folds of the labia majora and minora during baths or showers; and avoidance of douching, chemical irritants, and perfumed or deodorant soaps is crucial advice for young women.

If testing for sexually transmitted infections (STIs) (either due to abuse or sexual activity) is indicated, a speculum examination is not required to obtain an endocervical specimen given the current availability and efficacy of urine-based gonorrhea and chlamydia nucleic acid amplification testing (NAAT).[24] The recently revised 2009 ACOG guidelines for cervical cancer screening state that the first Pap test should be performed at age 21 years regardless of the age of first intercourse.[25] The exception to this general rule is if the patient has HIV and is sexually active, initial screening should include a Pap test and pelvic exam; the Pap test should be obtained twice during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter.[26]

If necessary to evaluate abnormal bleeding or other pathology in a young teen, a narrow Pederson speculum may be used to visualize the cervix and vaginal mucosa. To assess a possible pelvic mass, a young adolescent, even one who has never been sexually active, may undergo a single digit bimanual exam or rectal exam.

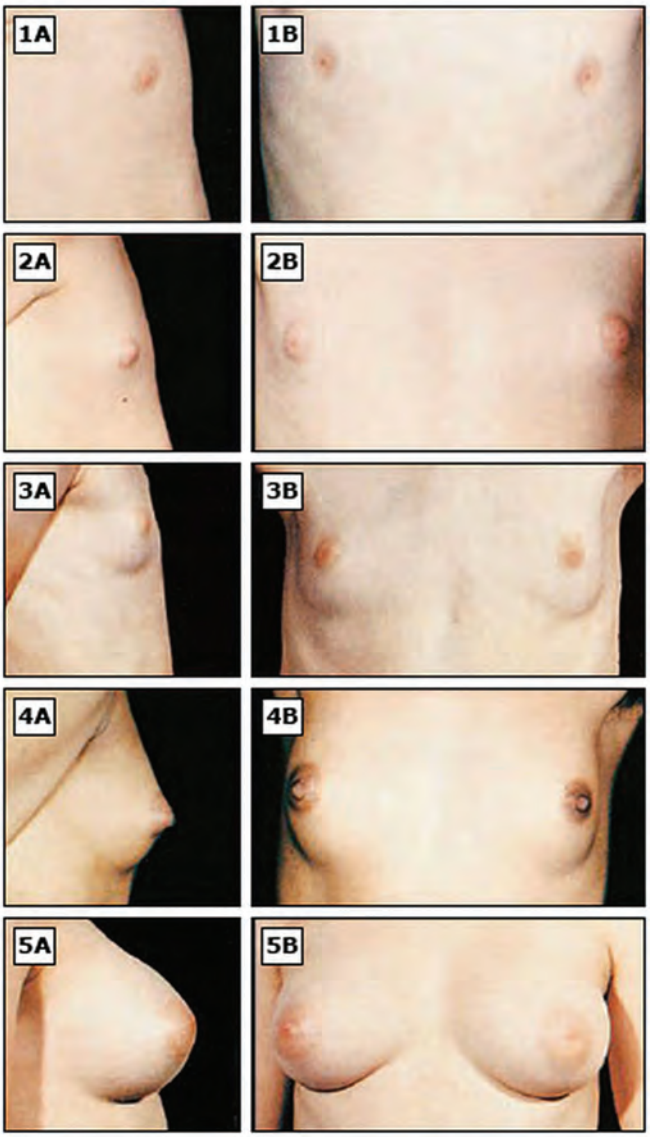

FIGURE 23.9 Sexual maturity rating (Tanner staging) of breast development in girls. Stages in breast development in girls. *Stage 1*: Prepubertal, with no palpable breast tissue. *Stage 2*: Development of a breast bud, with elevation of the papilla and enlargement of the areolar diameter. *Stage 3*: Enlargement of the breast, without separation of areolar contour from the breast. *Stage 4*: The areola and papilla project above the breast, forming a secondary mound. *Stage 5*: Recession of the areola to match the contour of the breast; the papilla projects beyond the contour of the areola and breast. (Reproduced from Roede MJ, van Wieringen JC. Growth diagrams 1980: Netherlands third nation-wide survey. *Tijdschr Soc Gezondheids.* 1985;63:1, with permission.)

Alternatively, a transabdominal ultrasound may be used to document internal genital structures as long as the bladder is well-filled.

Anemia and iron deficiency are common among adolescent girls, reflecting the changes in hemoglobin and serum ferritin concentrations, which are influenced by both sex and pubertal stage. Both hemoglobin and serum ferritin concentrations increase in adolescent boys but not in girls; coupled with menstrual bleeding and insufficient anemia, this predisposes pubertal girls to anemia.[27]

VULVAR DISORDERS

Vulvovaginitis

Vulvovaginitis is the most common indication for referral to a pediatric gynecologist, is the most common gynecologic problem in prepubescent girls, and is often the result of poor hygiene or chemical irritants in combination with prepubertal vulvar anatomy.[28] Prepubertal genital tissues are vulnerable to infection and irritation because there are no protective lactobacilli, the alkaline state of the vagina (pH 7), poor labial development, and the tissues are thin due to the low estrogen state. Additionally, the distance from the anus to the vestibule is comparatively short, and fecal pathogens easily access the vagina.

Symptoms and signs of vulvitis include pruritus, tenderness, dysuria, and erythema of the vulva. The presence of discharge is more indicative of a vaginitis, which is inflammation of the vagina. These two diagnoses may occur simultaneously. The differential diagnosis of vulvovaginitis in children and adolescents includes infections, vaginal foreign bodies, pinworms, trauma, lichen sclerosus, psoriasis, eczema, contact dermatitis, scabies, ectopic ureter, sexual abuse, congenital abnormalities, chronic masturbation, and commonly, poor genital hygiene. Nonspecific vulvovaginitis is vulvovaginal irritation without an identifiable bacterial pathogen, and it accounts for 25 to 75% of all cases.[29] Parents and children need to understand the importance of proper hygiene in the prevention of vulvovaginitis. Carefully washing between labial folds with a nonirritating soap may prevent complaints of pain or itching in the genital region. The child should avoid soaking in a tub with shampoo or bubble bath because these may cause chemical irritation. However, soaking in warm clean bathwater for 15-minute intervals is soothing and helps with cleaning the area. We emphasize wiping from front to back (from urethra toward anus) to minimize contamination of the vulva and vagina with enteric organisms, and encourage the use of a wet wipe (front to back) after bowel movements for girls who have difficulty with recurrent vulvovaginitis. Time spent in tight-fitting clothing such as tights, leotards, and swimsuits should be minimized; loose-fitting cotton undergarments and clothing are preferred. Sleeping in nightgowns without underwear in lieu of pants or sleeper pajamas are preferable because they allow the air to circulate. Undergarments should be washed with a mild, unscented detergent, and fabric softeners should not be used. Thong underwear can promote fecal contamination of the vagina and should be discouraged. Spending prolonged periods of time in wet bathing suits should be avoided.

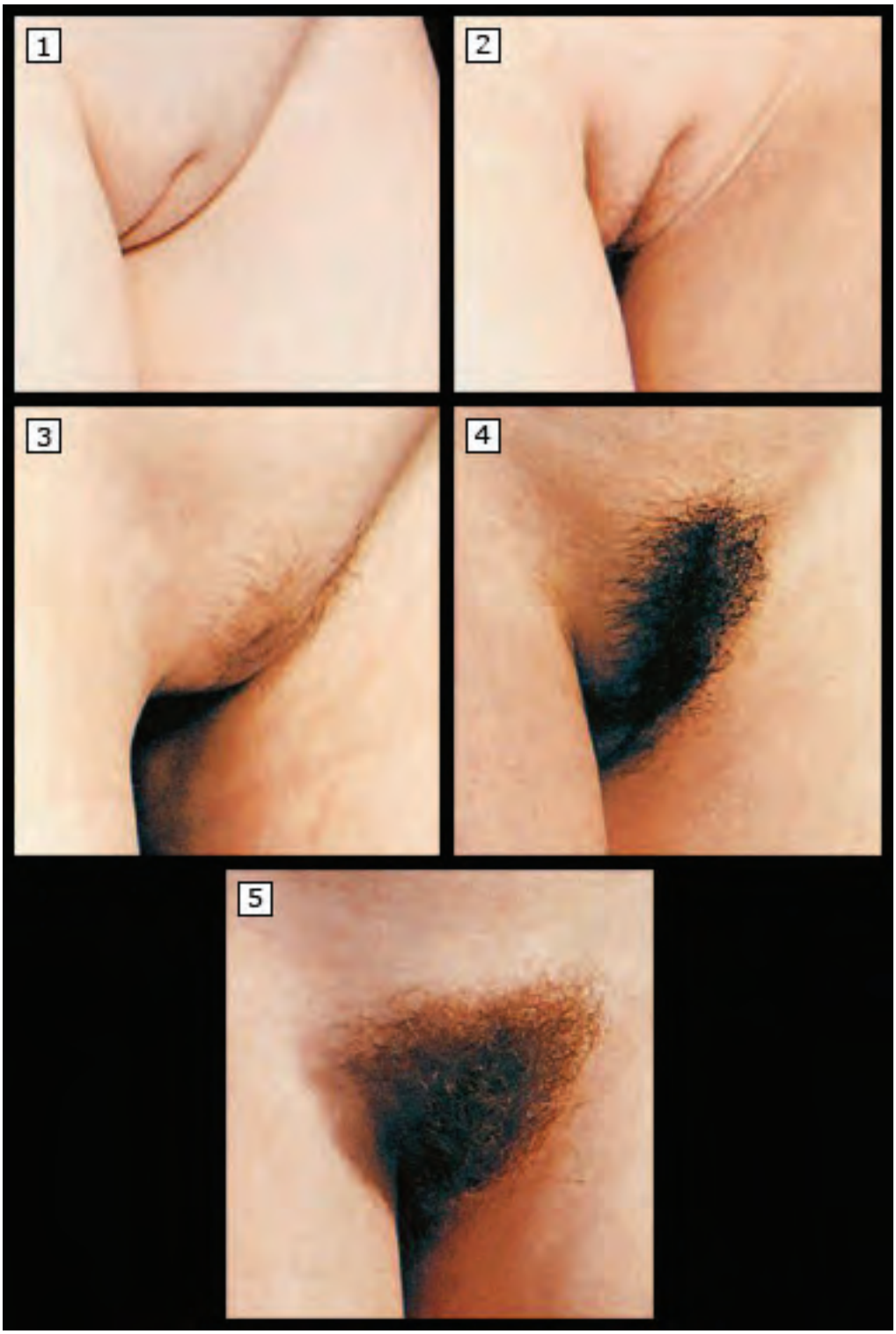

FIGURE 23.10 Sexual maturity rating (Tanner staging) of pubic hair development in girls. Stages of development in pubic hair in girls. *Stage 1*: Prepubertal with no pubic hair. *Stage 2*: Sparse, straight hair along the lateral vulva. *Stage 3*: Hair is darker, coarser, and curlier, extending over the mid-pubis. *Stage 4*: Hair is adult-like in appearance but does not extend to the thighs. *Stage 5*: Hair is adult in appearance, extending from thigh to thigh. (Reproduced from Roede MJ, van Wieringen JC. Growth diagrams 1980: Netherlands third nation-wide survey. *Tijdschr Soc Gezondheids.* 1985;63:1, with permission.)

In a pediatric population, infectious vulvovaginitis, where a specific pathogen is isolated as the cause of symptoms, may be caused by fecal or respiratory pathogens. Cultures most commonly reveal *Escherichia coli*; Group A beta-hemolytic *Streptococci* (*Streptococcus pyogenes*) or *Haemophilus influenzae*. Other respiratory pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Branhamella catarrhalis*, and *Neisseria meningitidis*. Other fecal organisms that may be cultured include *Shigella* and *Yersinia*. *Streptococcus pyogenes* is the most commonly identified pathogen in prepubertal girls (up to 20%).[30] These organisms are generally transmitted by hand to the genital area as a result of poor hand washing or improper toilet hygiene. A specific antimicrobial treatment should be used only if predominant growth of a pathogen is identified.[31] Some clinicians will use an antibiotic if there is purulent discharge, other diagnoses have been excluded, and cultures are negative; choices include a 7- to 10-day course of amoxicillin, amoxicillin-clavulanate, topical clindamycin, or topical metronidazole. In adolescents who are sexually active, sexually transmitted pathogens may cause vaginitis (gonorrhea, chlamydia, and *Trichomonas*).

Pinworms may cause vulvar symptoms such as intense nocturnal itching. Children with recurrent vulvar complaints and/or who have perianal itching should be examined for pinworms. Mycotic infections (yeast), which may be a cause of diaper rash vulvitis, are an unlikely cause of vaginitis, occurring in only 3 to 4% of prepubertal children. The alkaline pH of the prepubertal vagina does not support fungal infections. *Candida albicans* vaginitis is more common in postpubertal girls and women. It is a commensal fungus that inhabits the skin and mucous membranes (mouth, nose, gastrointestinal tract, and postpubertal vagina). Risk factors for candidal infections include antibiotic use, which alters the bacterial flora of the vagina, hormonal contraceptives, use of vaginal sponges and diaphragms, sexual activity, pregnancy, diabetes, and any immunocompromised state. *Candida* infections may result in itching, pain with urination or intercourse, vulvar soreness or irritation, or reddened and swollen vulvar and vaginal tissues. Many teens assume that all vulvar itching and vaginal discharge is due to a yeast infection and self-medication with over-the-counter products. Incorrect self-diagnosis can lead to delay in receiving the proper treatment and may make the symptoms worsen. When evaluating vaginal discharge, the amount, color, and odor should be assessed.

Foreign bodies may cause acute as well as chronic recurrent vulvovaginitis and may be associated with chronic vaginal discharge, bleeding, spotting, and a foul-smelling odor. The child may not acknowledge or recall placing a foreign body in her vagina. Toilet paper is the most common foreign body found in children but other objects commonly found in households such as pen caps, buttons, and hairpins or bands may also be used. Imaging with x-ray is often not helpful, unless the foreign body is radiopaque. Toilet paper may be removed with a Calgi swab or, alternatively, irrigation of the vagina with sterile water or saline in the office may be helpful in flushing out small foreign bodies, particularly in the distal third of the vagina in a cooperative child. Diagnosis often necessitates an exam under anesthesia with vaginoscopy to visualize the entire vaginal canal. The foreign body may be removed with forceps under direct visualization. A vaginal polyp or tumor may present with vulvovaginal complaints such as discharge or discomfort. Sarcoma botryoides may involve the hymen, lower urethra, or anterior vaginal wall and its peak incidence is between 2 and 5 years of age. Benign polyps of the vagina and hymen area are rare but have been known to occur. Pelvic examination under anesthesia, vaginoscopy, and possibly cystoscopy may be necessary to determine the etiology and indicated treatment of the complaints.

Lichen Sclerosus

Lichen sclerosus (LS) is a vulvar lesion that presents with vulvar pruritus, irritation, dysuria, and sometimes bleeding. Its etiology is uncertain. Girls may present with itching, discomfort or pain in the vulvovaginal area, bleeding, discharge, and possibly bowel or bladder symptoms. Examination will reveal hypopigmentation of the skin surrounding the labial, clitoral, and perianal regions. Biopsy in children is rarely required to make the diagnosis; it may be made clinically. Although LS may be associated with underlying malignancy in adult women, this does not appear to be true for prepubertal girls. The mean age at diagnosis in children is between 5 and 7 years old.[32] Scratching can lead to petechiae, punctuate hemorrhagic areas, or blood blisters. In untreated cases, the vulvar anatomy can be lost due to scarring. A clitoral entrapment syndrome has been described wherein scarring of the clitoral hood may entrap underlying glands, resulting in pain when the clitoris becomes engorged or when there is sexual excitation.[33] Occasionally this may require surgical repair, but this is associated with a risk of postoperative scarring.

A common treatment regimen is clobetasol propionate 0.05% ointment (a potent corticosteroid) for use once or twice daily for 2 weeks to 1 month, followed by alternate-day usage for 1 month, and thereafter usage once or twice weekly to prevent disease flares.[34] A very small amount placed as a thin film of ointment is all that is needed. Once symptoms are under control, the patient may also be completely tapered off the drug unless therapy is required for a flare-up. Sudden cessation of the steroid ointment may lead to a rebound phenomenon. Recently, tacrolimus 0.1% ointment has been used successfully in a few prepubertal girls[35]; more studies are needed. If nocturnal scratching is a problem, an antihistamine may be given at bedtime. It has been

hypothesized that LS resolves spontaneously or improves during puberty; one study reported a 75% improvement of symptoms at menarche, with only 30% concomitant improvement in physical signs.[36] However, recurrences are common, and more long-term follow-up is needed to better determine the course of LS after puberty.

Genital Ulcers

Nonsexually transmitted vulvar ulcers, also called Lipschutz ulcers, aphthous ulcers, or virginal ulcers, may be seen in girls between ages 10 and 15 years.[37] They may also appear after an acute systemic viral infection such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), or influenza A.[38–40] These lesions are characterized by the development of painful shallow ulcers on the mucosal surfaces of the labia minora, accompanied by a purulent vaginal discharge and may be accompanied by systemic symptoms such as fatigue, malaise, fever, or headache. Patients with acute genital ulcers (AGUs) often present with or report severe dysuria. These young patients are often mistakenly diagnosed as having herpes simplex virus (HSV), although the clinical appearance of the ulcers is different and in most cases, the ulcers occur prior to genital or oral sexual activity (Fig. 23.11). An HSV culture is recommended although it is usually negative. AGU can be treated with topical anesthetics (e.g., lidocaine jelly), topical or systemic corticosteroids, and in more severe cases, oral or parental opioid analgesics.[41,42]

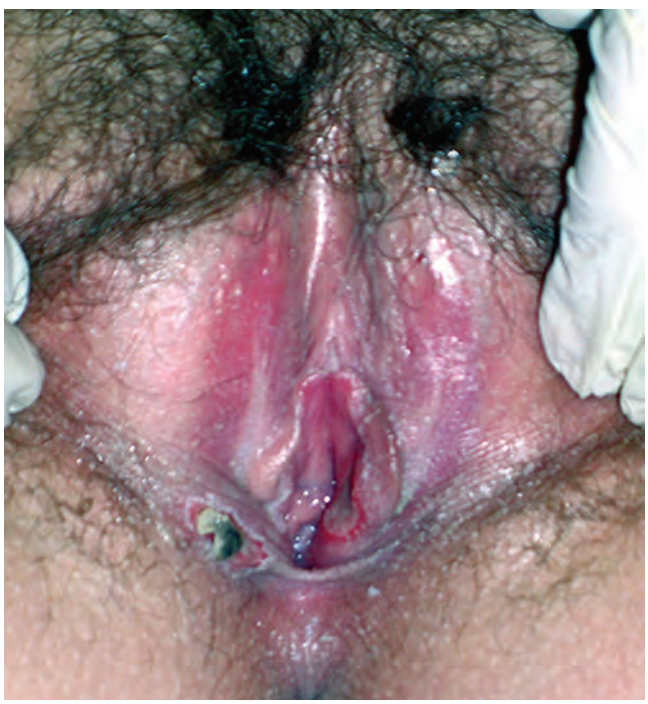

FIGURE 23.11 Vulvar ulcers. (Reproduced from Emans SJ, Laufer MR, eds. *Pediatric and Adolescent Gynecology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2012, with permission. Copyright © 2012 Lippincott Williams & Wilkins.)

If the patient cannot urinate due to pain or swelling, admission to the hospital and placement of a Foley catheter are necessary to avoid urinary retention. It is important that women with AGU receive ongoing weekly follow-up until the ulcer(s) has re-epithelialized and pain has resolved. Mean time to healing is reported as 16 to 21 days (range 5 to 52 days).[43] If the lesions recur, particularly in the setting of oral aphthae and visual complaints and arthritis, an immunologic workup is indicated to exclude Behçet disease.

In contrast to the aphthous AGUs described earlier, genital HSV is sexually transmitted or autoinoculated. These patients present with multiple painful vesicular or ulcerative lesions of the vulva often associated with swelling, a purulent discharge, and dysuria. During the first episode, 50 to 75% of patients have systemic symptoms including fever, malaise, headache, myalgias, and bilateral tender inguinal lymphadenopathy. The majority of genital lesions are caused by HSV-2; however, autoinoculation from HSV-1 can occur. The virus is usually shed from active lesions, but viral shedding in the absence of clinical symptoms or in people unaware of their infectious status accounts for almost 70% of all genital HSV-2 infections.[44] Polymerase chain reaction (PCR) assays for HSV DNA are the most accurate means of diagnosis. Treatment is with analgesics and oral antiviral medication.

Labial Adhesions

Labial adhesions (also referred to as labial agglutination or labial synechiae) are usually discovered by a parent or provider on routine physical exam. The precise etiology of labial adhesions is not known, but it is likely associated with a hypoestrogenic state and poor genital hygiene, which leads to inflammation, labial adherence, urinary dribbling, and more irritation. The adhesions may be partial or complete. On physical exam, the vagina may appear "absent," but actually, a thin opaque line may be visible where the labia are fused. Some children are asymptomatic, whereas others will present with vulvar inflammation, dysuria or recurrent urinary tract infections, or recurrent vaginal infections. If the adhesions are asymptomatic, do not affect the urine stream, and involve only a small portion of the labia, treatment is usually not necessary.

Mild asymptomatic cases may simply be observed, and the caregiver should be instructed in genital hygiene with gentle separation of the labia to cleanse the vaginal area. In more severe cases, for example, there is disruption or alteration of the urine stream, or if treatment is desired, gentle application of a topical estrogen cream directly on the line of adhesions once or twice daily will thin and eventually separate the adhesions. Use of estrogen must be discontinued if breast budding occurs. The time course to resolution depends on the compliance with this regimen and the thickness of the adhesions

but ranges from 1 to 8 weeks.[45] Following separation, a transition to a daily emollient may be made (e.g., A&D ointment or white petrolatum jelly) for at least 1 month (longer may be preferable) to prevent re-agglutination. In addition, good perineal hygiene is essential for these children.

Conservative therapy for labial adhesions may occur if the adhesions are thick (3 to 4 mm in width) and have no thin, obvious raphe or if the estrogen cream was placed in the wrong location or too little is used.[46] In the rare case, where medical treatment fails or acute urinary retention exists, surgical separation of adhesions (with anesthesia) may be offered, but the adhesions should never be incised or torn apart without anesthesia and postoperative pain management. Postoperatively, topical estrogen should be used for 1 to 2 weeks and a bland emollient should be used for the next 6 to 12 months. Most adhesions resolve or do not reoccur after endogenous estrogen production at puberty.

EVALUATION OF PREPUBERTAL VAGINAL BLEEDING

Vaginal bleeding in childhood is relatively rare and thus requires immediate evaluation to rule out significant pathology such as trauma or a genital tract neoplasm. Bleeding from the endometrium may be seen in the newborn as a result of withdrawal from maternal estrogen. Iatrogenic causes, such as overuse of estrogen cream for treatment of labial adhesions or accidental ingestion of prescription medication containing estrogens, may also lead to prepubertal bleeding.

Specific organisms or infections associated with vaginal bleeding include *Shigella* (bloody vaginal discharge and bloody diarrhea), *Streptococcus pyogenes* (group A beta hemolytic *Streptococcus*), and condylomata acuminatum (if friable).

Group A streptococcal vaginitis is associated with a purulent vaginal discharge that is blood tinged about half of the time and there is a fiery red or beefy appearance to the perineal skin that is well demarcated.[47] Although most patients do not have symptomatic pharyngitis, cultures of the throat are positive in about 75% of cases. *Shigella* vaginitis produces a discharge that is bloody or serosanguinous in about 50% of cases and there is a concurrent vulvitis.[48] Only 33 to 50% of patients have a history of recent or concurrent diarrhea and stool cultures are generally negative.

Disorders of the urinary tract, such as urinary tract infections and gross hematuria, may initially be misinterpreted as vaginal bleeding by concerned parents. Urethral prolapse, a partial or complete circular eversion of the urethral mucosa, presents as a painless bleeding annular lesion above the introitus. Children usually complain of bleeding, dysuria, and/or difficulty with urination. Treatment consists of twice-daily sitz baths, topical estrogen cream, and antibiotics if an infection coexists. Urethral prolapse usually resolves in 4 to 6 weeks.[49] If the prolapse persists, there may be an underlying urethral polyp. Rarer urologic abnormalities such as urethral neoplasms may also present as "vaginal bleeding."

Neoplasms of the genital tract often present with vaginal bleeding, and although rare, must be excluded as a cause of any prepubertal vaginal bleeding. Vaginal polyps should be removed and examined by pathology to exclude malignancy. Endodermal sinus tumors and rhabdomyosarcomas (sarcoma botryoides) occur almost exclusively in girls younger than the age of 3 years with vaginal bleeding.[50] Embryonal rhabdomyosarcomas (also known as sarcoma botryoides) are malignant cystic masses that can be found in the vagina, cervix, hymen, and urethra. They appear as a friable polypoid tumors originating from the submucosal tissues and spreading beneath the epithelium, causing the mucosa to bulge. Definitive diagnosis requires tissue biopsy, and once the diagnosis is made, collaboration with pediatric oncologists is recommended for appropriate treatment.[51]

Hemangiomas are benign growths of blood vessels that generally are small at birth, then proliferate for several months and ultimately involute or may resolve with puberty. If they are intravaginal, they may cause bleeding and may require intervention.[52] Surgical intervention should be undertaken in partnership with a vascular surgeon. Care should be taken not to confuse them with evidence of sexual abuse.

Benign isolated ovarian follicles in the prepubertal child may result in endogenous estrogen production, breast development, and endometrial proliferation. When the spontaneous follicles resolve, the child may present with vaginal bleeding. Ovarian granulosa cell tumors are the most common malignant tumor that produces signs of precocious puberty. These may present as a painful abdominal mass and are known to produce estrogen, thereby causing secondary sexual development and vaginal bleeding in children. Surgery consisting of a unilateral salpingo-oophorectomy is usually curative. Management of such ovarian lesions requires expertise to prevent over- or undertreatment.

Hypothyroidism in the prepubertal child may present with growth delay, signs of precocious puberty, ovarian cysts, and/or vaginal bleeding.[53]

SEXUALLY TRANSMITTED INFECTIONS

STIs (gonorrhea, chlamydia, and *Trichomonas*) may cause vaginal discharge or vulvovaginal irritation. STIs diagnosed in children should raise a suspicion for sexual abuse and prompt further evaluation.[54] Although the identification of sexually transmissible agents in children beyond the neonatal period suggests sexual abuse, exceptions do occur. Children may acquire these infections via vertical transmission from their mothers during childbirth.[55] Perinatally acquired rectal or vaginal *Chlamydia*

trachomatis infection may persist for 2 to 3 years after birth.[56] *Trichomonas vaginalis* infection may occur in newborns but is rare in prepubertal children; if it is identified in children, sexual contact is the likely etiology.

Based on the 2009 Youth Risk Behavior Survey (YRBS), approximately half of U.S. adolescents attending high school have been sexually active, placing them at risk for STIs.[57] Nationwide, 5.9% of students reported having sexual intercourse for the first time before age 13 years.[58] The incidence of STIs among persons aged 15 to 24 years is estimated at 9.1 million cases. Estimates suggest that even though young people aged 15 to 24 years represent only 25% of the sexually experienced population, they acquire nearly half of all new STIs. In 2009, as in previous years, women aged 15 to 19 years had the highest rates of chlamydia and gonorrhea compared with any other age or sex group.[24]

Sexually active adolescents aged 15 to 19 years are at higher risk of acquiring STIs due to a combination of behavioral, biological, and cultural reasons. Factors contributing to this increased risk during adolescence include having multiple sexual partners concurrently, having sequential sexual partnerships of limited duration, and failing to use barrier protection consistently and correctly.[59] Adolescent females may have a physiologically increased susceptibility to infection with gonorrhea and chlamydia because of increased cervical ectopy. The higher prevalence of STIs among adolescents also may reflect multiple barriers to accessing quality STI prevention services, including lack of insurance or other ability to pay, lack of transportation, discomfort with facilities and services designed for adults, and concerns about confidentiality. Parental consent may be waived for minors seeking diagnosis and treatment of STIs in most states, but providers should be knowledgeable about specific state mandates. Sexual health discussions should be incorporated into the medical visit for all adolescents. Such discussion should be appropriate for the patient's developmental level and identify risk behaviors (e.g., unprotected oral, anal, or vaginal sex and drug-use behaviors). Careful, nonjudgmental, and thorough counseling is vital for adolescents who might not feel comfortable acknowledging their engagement in behaviors that place them at high risk for STIs.

Routine laboratory screening for *C. trachomatis* and *Neisseria gonorrhoeae* is recommended annually for sexually active adolescents, and HIV screening should be discussed and encouraged. The Centers for Disease Control and Prevention (CDC) also recommends that all women with chlamydia or gonorrhea infections, especially adolescents, be rescreened 3 to 6 months after treatment, because of the high prevalence of reinfection in this population.[60] Syphilis screening should also be done in certain situations, including a history of multiple sexual partners, IV drug use, and living in an endemic area.[61]

Treatment of all STIs is a rapidly changing area in medicine; providers should refer to the CDC website (www.cdc.gov/std/treatment) for the most up-to-date recommendations. For patients diagnosed with chlamydia or gonorrhea, the CDC supports expedited partner therapy, which is the clinical practice of treating the sex partners by providing prescriptions or medications to the patient to take to her partner. These patients should also be educated on the consequences of acquiring an STI. For example, pelvic inflammatory disease (PID) is an infectious process that involves the upper genital tract and has the long-term sequelae of chronic pain, adhesive disease, increased risk of ectopic pregnancy, and infertility.[62]

Human Papillomavirus

In prepubertal children, the presence of anogenital warts may be a marker of sexual abuse. However, the possibility of different modes of transmission (e.g., vertical transmission from mother to child, autoinoculation or heteroinoculation from cutaneous warts, or indirect transmission from fomites) has also been demonstrated and may be more likely than abuse in children younger than 3 years of age.[63] The mother may not be symptomatic or have a history of human papillomavirus (HPV) but vertical transmission may still occur. In over 50% of patients, there is spontaneous resolution within 5 years, so expectant management is a reasonable approach.[64] Families may choose to have them treated, however, but most treatment options have not been well studied in the pediatric population.

As with other STIs, HPV disproportionately affects adolescent and young adult women. In adolescents, risk factors for HPV infection include early age of first sexual intercourse, number of lifetime sexual partners, immunosuppression, and cigarette use.[65] In a recent study of women in the United States, 25% of 14- to 19-year-olds and 45% of 20- to 24-year-olds were infected with at least one type of HPV.[66] Despite the increased exposures to HPV, most (90%) HPV infections in adolescents will resolve without treatment within 2 years.[67] For this reason, the revised American Society for Colposcopy and Cervical Pathology (ASCCP) Consensus Guidelines recommend that cervical cancer screening with Pap tests not be initiated until 21 years of age, unless the patient has HIV or is otherwise immunocompromised. These guidelines also advise against HPV testing before age 30 years and recommend observation for the management of CIN 1 and CIN 2 if found due to inappropriate screening.[25] High-risk HPV types 16 and 18 are responsible for approximately 50% of cervical intraepithelial neoplasia (CIN) 3 lesions and 70% of cervical cancers.[68] Low-risk types, such as HPV 6 and HPV 11 are responsible for almost all cases of genital warts. Recommended treatments for genital warts include cryotherapy with liquid nitrogen, trichloroacetic acid (TCA), carbon dioxide laser therapy, and imiquimod cream (a topical immunomodulator).

In 2006, a quadrivalent vaccine was approved by the U.S. Food and Drug Administration (FDA) for

vaccination against HPV types 6, 11, 16, and 18; and in 2009, a bivalent vaccine was approved by the FDA for vaccination against HPV types 16 and 18. Both vaccines demonstrated 90 to 100% efficacy in preventing persistent HPV infection, CIN 2/3, and adenocarcinoma in situ caused by HPV-16 and -18 among women who had not previously been infected by those HPV types.[69] For this reason, both the CDC and the ACOG currently recommend routine vaccination of girls between 11 and 12 years of age, although vaccination may be administered as early as age 9 years.[70] The Advisory Committee on Immunization Practices (ACIP) also recommends vaccine administration to all previously unimmunized female patients aged 13 through 26 years.[71]

CONTRACEPTIVE OPTIONS

Sexual activity along with inconsistent contraceptive use contributes to the high rate of adolescent pregnancy in the United States, which exceeds that of other industrialized nations.[72] Thus, another important focus of the adolescent gynecology appointment should be counseling on the currently available contraceptive methods. Most adolescents use oral contraceptives and condoms for contraception, although they have been found to have higher continuation rates and decreased contraceptive failure rates with longer acting contraceptive methods such as implants or intrauterine devices (IUDs).[73,74] Although condoms are an extremely important method of protection for adolescents because they also protect against STIs, patients should be aware that the contraceptive failure rate for male condoms is 18% with typical use.[75] Thus, sexually active adolescents should be encouraged to use condoms in conjunction with a more effective method of contraception.

Oral contraceptive pills (OCPs) containing a combination of estrogen and progesterone have a beneficial effect on a number of conditions that affect an adolescent's quality of life, including dysmenorrhea, acne, and menstrual irregularity.[76] Emphasizing these health benefits to adolescents may contribute to more consistent and correct use of OCPs. Any time combination oral contraceptives are prescribed, possible side effects of hormonal therapy must be explained, including nausea, vomiting, spotting, breakthrough bleeding, and the rare possibility of a venous thromboembolic event. Thoroughly counseling patients on common adverse effects helps to minimize patient anxiety and maximize compliance with OCPs. For example, adolescents should be counseled that breakthrough bleeding is common in the first months of use, is not medically harmful, frequently is caused by missed pills, and tends to resolve within a few cycles. Compliance with OCPs in adolescents remains a substantial problem. The use of a daily cell phone alarm aids in reminding many teens to take their pill at the same time every day. Other contraceptive delivery systems such as intrauterine, subdermal, injectable, transvaginal, and transdermal can be used by most adolescents and may improve adherence. Long-acting reversible contraceptive (LARC) methods may be more appropriate than estrogen-containing methods in adolescents with certain medical conditions, namely hypertension, systemic lupus erythematosus associated with antiphospholipid antibodies, and migraines with aura.[77]

Both the Copper T380A intrauterine device (CuT380A) and the Levonorgestrel intrauterine system (LNG-IUS) provide safe, long-term contraception that is not patient compliance dependent. Despite the reluctance of many physicians to provide nulliparous young women with intrauterine contraception, nulliparity is not a contraindication for an IUD. The ACOG advocates use of long-acting reversible contraception to decrease unintended pregnancy stating that implants and intrauterine contraception should be encouraged for all appropriate candidates, including nulliparous women and adolescents.[78] Difficult or painful IUD insertion is another concern for adolescents. Paracervical blocks and nonsteroidal anti-inflammatory drugs may improve insertion-related pain, and misoprostol pretreatment may increase the ease of insertion.[79]

Depot medroxyprogesterone acetate (DMPA) is an intramuscular injection given once every 3 months. The two most commonly reported adverse side effects associated with use of this contraceptive agent are weight gain and loss of bone mineral density (BMD). Overall, weight gain is reported in up to 54% of adolescents receiving DMPA. However, recent research indicates that this body weight (mainly in the form of body fat) may override the potential detrimental effect on bone seen with the use of DMPA.[80] Additionally, any observed short-term losses in BMD may be recovered and are unlikely to place women at risk of fracture.[81] There does not appear to be a decrease in BMD with the single-rod etonogestrel implant because normal levels of estrogen are maintained with this device.[82] Both of these methods may cause irregular bleeding, and this is the most common adverse event leading to discontinuation.

Adolescents should also be counseled about emergency contraceptive methods, which should be taken as soon as possible up to 3 to 5 days after unprotected intercourse (depending on the specific medication used). If they are age 17 years and older, they should be informed that emergency contraception is available over the counter. If they are younger than 17 years of age, an advance prescription may be provided. The legal right of minors to obtain confidential services for contraception varies according to state law.

MENSTRUAL DISORDERS IN THE ADOLESCENT

Diagnosis

Abnormal uterine bleeding and menstrual disorders are common in early adolescence (Table 23.3). Menorrhagia

TABLE 23.3 Causes of Abnormal Uterine Bleeding in the Adolescent Girl

Anovulatory uterine bleeding	Blood dyscrasia
Pregnancy-related problems	Thrombocytopenia
Threatened, spontaneous, incomplete, missed AB	Clotting disorders
Problems with termination procedures	Liver disease
Ectopic pregnancy	Endocrine disorders
Gestational trophoblastic disease	Anovulatory bleeding
Infection	Thyroid disease
Pelvic inflammatory disease	Adrenal disorders
Endometritis	Hyperprolactinemia
Cervicitis	Polycystic ovary syndrome
Vaginitis	Ovarian failure
Vaginal abnormalities	Ovarian problems
Carcinoma	Cyst
Lacerations	Tumor
Cervical problems	Endometriosis
Cervicitis	Trauma
Polyp	Foreign body
Hemangioma	Systemic disease
Carcinoma	Diabetes mellitus
Uterine problems	Renal disease
Submucous myoma	Systemic lupus erythematosus
Congenital anomalies	Medications
Polyp	Hormonal
Carcinoma	Anticoagulants, platelet inhibitors
IUD	Androgens, spironolactone
Breakthrough bleeding	Antipsychotics
Ovulatory bleeding	

AB, abortion; IUD, intrauterine device.

From De Silva NK. Definition and evaluation of abnormal uterine bleeding in adolescents. UpToDate Web site. http://www.uptodate.com/contents/definition-and-evaluation-of-abnormal-uterine-bleeding-in-adolescents. Accessed December 17, 2013; adapted from Emans SJ. Dysfunctional uterine bleeding. In: Emans SJ, Laufer MR, eds. *Pediatric and Adolescent Gynecology.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:270.

is defined as heavy menstrual bleeding lasting for more than 7 days or product use of greater than six pads or tampons per day.[83] In clinical practice, it is difficult to quantify menstrual blood loss; one variable that predicts significant blood loss is the need to change a thick pad or super tampon more than hourly to prevent staining clothing. In the assessment of young patients with a complaint of heavy periods, the clinician should also take into consideration the impact of menses on the teenager's life; for example, missed days of school and inability to participate in sporting and social activities may be indications for medical management. For young women with intellectual and physical disabilities, relatively normal periods may pose a serious problem with regard to managing menstrual hygiene.

When an adolescent presents with menorrhagia, it may be a sign of an underlying bleeding condition. Prevalence rates for von Willebrand disease are estimated at 5 to 20% and 1 to 47% for platelet disorders in adolescents presenting with excessively heavy menses.[84] Such patients may relate a family history of heavy bleeding or a known bleeding disorder, and symptoms of epistaxis, easy bruisability, or gingival bleeding. Physical examination findings suggestive of a bleeding disorder may include bruising, ecchymoses, and pallor. Initial laboratory testing should include a complete blood count to assess for hemoglobin level and to exclude thrombocytopenia. Other lab tests that should be part of the evaluation include a peripheral smear, platelet function analysis, plasma von Willebrand factor (vWF) antigen, plasma vWF activity (ristocetin cofactor activity), factor VII activity, blood group typing (blood group O is associated with lower levels of vWF), and a thyroid-stimulating hormone (TSH). A prothrombin time (PT) and an activated partial thromboplastin time (aPTT) should also be part of an initial screen.[85] vWF antigen and platelet function assays should be considered if the initial screening tests are abnormal. Estrogens will increase vWF, so obtaining laboratory testing prior to initiating hormonal treatment is important. Referral to a hematologic specialist may be needed for further investigation to determine the presence of rare factor deficiencies.

Another very common abnormality of uterine bleeding is irregular menses (metrorrhagia). Normal menstruation lasts 7 days or fewer, is associated with about 80 mL or less of blood loss with each cycle, and although it often occurs at 28-day cycles, if it occurs regularly every 22 to 44 days, this is also normal. Irregular bleeding that is less than normal, normal, or more than normal is referred to as menometrorrhagia. This may present as bleeding too frequently (menses <28 days apart) or polymenorrhea, or not frequently enough (menses >35 days apart), referred to as oligomenorrhea. Anovulation is the most common cause of abnormal uterine bleeding in adolescents in the first 1.5 to 2 years after menarche and due to an immature hypothalamic-pituitary-ovarian (HPO) axis or polycystic ovarian syndrome (see next section on endocrine abnormalities) is the likely cause in the majority of cases of both irregular and heavy bleeding. Unopposed estrogen stimulation results in an unstable endometrial lining, which sheds irregularly. Once menarche occurs, ovulatory cycles may take up to 3 years to become established.[86] However, other endocrine disorders must be ruled out, including thyroid disease and hyperprolactinemia.

Adolescents should be encouraged to keep a menstrual calendar, beginning with menarche. This will help them be aware if irregularities begin to occur in their cycles, as well as to anticipate menstrual symptoms and, if necessary, initiate therapy for conditions such as dysmenorrhea a day before menstruation starts. It is important to let the patient know that if abnormal uterine bleeding is heavy or prolonged, this may lead to anemia and that missing cycles for prolonged periods of time (more than 2 to 3 years) may increase the risk of uterine cancer.

Also important in the differential diagnosis for abnormal uterine bleeding in an adolescent are pregnancy and infection (cervicitis). Diagnostic sonography can

determine if a uterine abnormality is present or if the endometrium is thick or thin. Structural lesions in the adolescent uterus such as fibroids or polyps are extremely rare. The patient should also be asked about past and present medication usage because DMPA, IUDs, and missing daily birth control pills may be associated with abnormal bleeding patterns.

The absence of menstrual periods, amenorrhea, can be categorized as primary amenorrhea (no menses by age 16 years) and secondary amenorrhea (cessation of previously established menstrual periods). A pregnancy test (serum or urine) should always be done when evaluating any adolescent patient with amenorrhea. Common causes for amenorrhea include pregnancy, eating disorders, strenuous exercise, weight loss, and stress. Women vary in their susceptibility to inhibition of the reproductive axis by such stressors, and there is emerging evidence that there may be a genetic predisposition to developing hypothalamic amenorrhea as a result of changes in GnRH secretion.[87] Anatomic defects and primary ovarian insufficiency must also be considered in the differential diagnosis of amenorrhea (see section on Anatomic Abnormalities).

A thorough history, including family history around menstruation, infertility, bleeding disorders, and thyroid issues should be obtained. The physical exam should include height, weight, and arm span, examination of the thyroid, inspection for signs of androgen excess, Tanner staging, breast exam looking for galactorrhea, and abdominal examination to rule out a uterine or ovarian mass. An external examination of the genitalia should be done for all patients. This should note the stage of adrenarche, clitoral size, health of the vulvar tissues and perineal and anal areas, and the vaginal introitus and hymen. A pelvic examination should be done if it is tolerated but, if not, it may be deferred until after a trial of medical therapy or a pelvic ultrasound may be considered to gather additional clinical information. Adolescents with abnormal uterine bleeding should have a pregnancy test, a hemoglobin/hematocrit and platelet count measurement, and a TSH level. Further laboratory testing should be ordered as indicated by the history and physical examination findings.

Management

There are currently no randomized controlled trials that specifically address how to treat menorrhagia in adolescents. If there is no anemia, patient stress is minimal, and the flow is only slightly to moderately increased, observation is appropriate. A menstrual calendar can be used to prospectively record the exact menstrual pattern. Hormonal therapy may be considered to stabilize proliferation of the endometrium as well as to establish cyclic shedding of the endometrium. Over 90% of adolescents will respond to hormonal treatment.[88] Hormonal methods, which have been shown to reduce menstrual blood loss in adults, include combination estrogen–progestin oral contraceptive pills (COCP), both cyclic and extended cycle use,[89] oral or injected progestins, or the LNG-IUS, all of which are accepted options for adolescents.[90] COCPs are often used as first-line treatment due to their effectiveness and ease of administration. Monophasic pills containing at least 20 mcg of ethinyl estradiol should be used initially and can be given once daily in the adolescent who is not actively bleeding.

If there is active bleeding, and no contraindications, estrogen should be used for, or at least a part of, hormonal control as it promotes hemostasis. If there is heavier or active bleeding, an OCP taper can be used. There are several regimens documented, but a common approach is to give one pill four times daily until bleeding stops, then one pill three times daily for 3 days, then one pill twice daily for 2 days, followed by one pill once daily.[91] Alternatively, if the patient's bleeding is being closely monitored and appears to be decreasing after the first dose, the taper to one pill daily can be done more rapidly. IV conjugated estrogen (25 mg every 4 to 6 hours) (without any progestin therapy) may be used to control bleeding in unstable patients who cannot take oral medications. No more than six doses should be given and the minimum effective dose should be used as pulmonary embolism is a known complication of IV estrogen. Antiemetic therapy may need to be given 1 hour prior to infusion in order to alleviate the known side effects of nausea and vomiting. If the bleeding is significant, the patient may need a blood transfusion and, if IV therapy does not slow the bleeding, possible surgical intervention with a dilation and curettage. Bleeding usually responds IV estrogen within 4 to 24 hours; if it lasts beyond 24 to 48 hours, oral progesterone may be added to help stabilize the endometrium. Once the bleeding stops, the patient may be switched to a combination OCP that has at least 50 mcg of estradiol in it for 1 to 3 months.

If combined OCPs are contraindicated, or the patient or family does not wish to start oral contraception, cyclic progestins can be used. Oral progestin-only methods may not reliably prevent ovulation and the adolescent must be aware of this so that if she is or becomes sexually active, she knows how to use other methods of contraception. Oral medroxyprogesterone 10 mg or norethindrone acetate 5 mg can be given for 10 to 14 days each month to induce a withdrawal bleed that is cyclic and predictable. Other options include micronized oral progesterone (200 mg) for the first 12 days of each month. This pattern may be continued for 3 to 6 months.[92] Therapy may be stopped then to determine if a normal menstrual cycle has been established. If irregular or heavy bleeding returns or persists during therapy, further evaluation may be undertaken. This may include measurement of prolactin, dehydroepiandrosterone sulfate, 17-hydroxyprogesterone, free and total testosterone, TSH, fasting insulin, and glucose levels.

Hemostatic therapies such as desmopressin, antifibrinolytics such as aminocaproic acid and tranexamic acid, and clotting factor concentrates should be considered in those

adolescents who have failed hormonal management.[84] Desmopressin is administered intravenously as 0.3 mcg/kg over 15 to 30 minutes; the dose may be repeated in 48 hours if there is no response and the nasal route is not recommended for acute bleeding. Aminocaproic acid may be given orally or intravenously. Oral aminocaproic acid is given as 5 g in the first hour, and then a continuing dose of 1 to 1.25 g per hour for approximately 8 hours or until the bleeding is controlled. If given intravenously, the dose of aminocaproic acid is 4 to 5 g IV in the first hour followed by 1 g per hour for approximately 8 hours or until the bleeding is controlled. Tranexamic acid (1 g four times daily, on days of heavy bleeding) has been demonstrated to reduce menstrual loss by 40% in adult women.[93] Although widely used in other countries, this drug has not yet been approved for women younger than 18 years of age nor studied in adolescents in the United States.

In certain cases, such as adolescents undergoing chemotherapy, thrombocytopenia associated with myelosuppression can be anticipated. Little data are available on preventative measures for uterine bleeding, but one option may be to give a GnRH agonist to induce amenorrhea. If leuprolide acetate is attempted, it should be administered 2 to 4 weeks prior to the expected onset of thrombocytopenia to avoid the "flare" effect, which may result in bleeding.[94] A retrospective study compared DMPA, a GnRH agonist and placebo, in women undergoing myelosuppressive chemotherapy. No menorrhagia was found in the women receiving the GnRH agonist, compared with 21% in the medroxyprogesterone group and 40% in the placebo group.[95]

ENDOCRINE ABNORMALITIES AND PUBERTY

Although its relevance is unknown, the HPO axis is active in infancy and peaks in activity between 6 and 8 weeks. Sex steroid levels at this time are comparable to those seen in early to mid-puberty but there are no peripheral effects. This is followed by a long period of active HPO axis inactivity, that is, prepuberty. Once the axis is reactivated, puberty ensues. Multiple mechanisms and pathways exist that may interfere with the normal processes of puberty.

Precocious Puberty

Precocious puberty is the onset of secondary sexual development before the age of 8 years in girls and 9 years in boys—these limits are 2.5 to 3 standard deviations below the mean age of onset of puberty. The mean age of pubertal onset is about 10.5 years of age for girls and 11.5 years of age for boys.[96] Evaluation is indicated in children who develop secondary sex characteristics younger than 8 years of age in girls and younger than 9 years of age in boys. The younger the age at presentation, the more extensive the evaluation should be and levels of concern should be high.

The mechanisms for precocious puberty include the following:

- *Central or GnRH dependent*: caused by early maturation of the HPO axis; idiopathic in over 80% of cases and most idiopathic cases occur in girls
- *Peripheral or GnRH independent*: peripheral or pseudoprecocious puberty is caused by excessive sex hormones from either the gonads, tumors, or exogenous sources; may cause either feminization or virilization in both girls and boys
- *Benign variants*: also referred to as incomplete precocious puberty and may result in isolated thelarche or adrenarche; monitoring is necessary because some cases progress to precocious puberty

To distinguish these mechanisms, a series of labs and imaging studies are often necessary (Tables 23.4 to 23.6). Diagnosis may require observation of the child's progression from one stage of pubertal development to the next in less than 3 to 6 months. Diagnostic studies include measurement of accelerated growth velocity demonstrated by growth charts and advanced bone age. Pelvic ultrasound

TABLE 23.4 Evaluation of Gonadotropin-Dependent ("Central") Precocious Puberty (GDPP)

Etiology	Gonadotropin Levels	LH Response After GnRH Stimulation	Sex Steroid Hormone Levels	Clinical Features	Additional Evaluation
Idiopathic (*80% of girls with GDPP*) or CNS tumor	Pubertal levels, with prominent LH pulses during sleep: LH >0.6 IU/L	Pubertal response: LH level post GnRH >7 IU/L	Pubertal values of estradiol (>9 pg/mL), testosterone (20–1200 ng/dL), and DHEAS	Pubertal development accelerated but proceeds in normal timing and sequence Enlargement of ovary/uterus (by ultrasound) or testes (by exam) Bone age >height age >chronological age Responsive to GnRH agonist therapy	Contrast-enhanced MRI of brain to rule out CNS abnormality In boys, measure hCG to exclude an hCG-secreting tumor Skin examination and skeletal survey to rule out McCune-Albright syndrome

LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone; CNS, central nervous system; DHEAS, dehydroepiandrosterone sulfate; MRI, magnetic resonance imaging; hCG, human chorionic gonadotropin.

From Saenger P. Definition, etiology, and evaluation of precocious puberty. UpToDate Web site. http://www.uptodate.com/contents/definition-etiology-and-evaluation-of-precocious-puberty. Accessed December 17, 2013.

TABLE 23.5 Evaluation of Gonadotropin-Dependent ("Peripheral") Precocious Puberty

Etiology	Gonadotropin Levels	LH Response After GnRH Stimulation	Sex Steroid Hormone Levels	Clinical Features	Additional Evaluation
Congenital adrenal hyperplasia (CAH) (untreated)	Prepubertal	Absent LH response	Sex hormone levels vary depending on the adrenal enzyme block	Boys have prepubertal testes with enlarged phallus and pubic hair development. Girls with "nonclassic" CAH may present with early pubic and/or axillary hair and other signs of androgen excess.	After therapy with glucocorticoids, GDPP may develop and require GnRH agonist therapy
Leydig cell tumor (boys)	Suppressed	Absent LH response	Very high levels of testosterone	Irregular and asymmetrical enlargement of testes	Tumor may not be palpable; testicular ultrasound aids in diagnosis
Ovarian cyst	Suppressed	Absent LH response	Normal or elevated estradiol; occasionally elevated androgens	Pubertal development accelerated; occasionally presents with ovarian torsion and abdominal pain	Abdominal ultrasound and/or MRI
hCG-secreting germ cell tumors (boys)	High hCG or positive pregnancy test	Absent LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm diameter (>4 mL volume), but smaller than expected for the degree of pubertal development Precocious puberty is seen only in boys as hCG only activates LH receptors (estrogen biosynthesis in the ovaries requires both FSH and LH receptor activation)	These tumors may occur in gonads, brain, liver, retroperitoneum, or mediastinum When in anterior mediastinum, a karyotype must be performed because of a strong association of this finding with Klinefelter syndrome
Familial male-limited (gonadotropin-independent) precocious puberty (boys)	Suppressed	Absent LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm diameter (>4 mL volume), but smaller than expected for degree of pubertal development; spermatogenesis may occur Familial: Male-limited autosomal dominant trait Precocious puberty is seen only in boys as there is only activation of the LH receptors, and ovarian estrogen biosynthesis requires both FSH and LH receptor activation	
McCune-Albright syndrome (girls>>boys)	Suppressed	Absent LH response	Pubertal values of estradiol in girls and testosterone in boys	Ovaries: Enlarged for age and usually containing multiple large cysts Testes: Symmetric and >2.5 cm diameter (>4 mL volume), but smaller than expected for pubertal development Skin: Multiple irregular-edged café-au-lait spots Bone: Polyostotic fibrous dysplasia	Ultrasound: Ovaries enlarged, with follicular cysts May have other hyperactive endocrine disorders: i.e., thyrotoxicosis and/or gigantism
Virilizing adrenal tumor	Suppressed	Absent LH response	High DHEA or DHEAS[a]; high androstenedione and testosterone	Testes prepubertal	CT, MRI, or ultrasound of adrenal glands to locate tumor; if still undetectable selective venous sampling of androgen
Adrenal cancer	Suppressed	Absent LH response	High DHEA or DHEAS[a]; high 17-ketosteroids in urine	May present with signs of glucocorticoid excess and may be associated with hereditary cancer syndromes	CT, MRI, or ultrasound of adrenal glands to locate tumor; if still undetectable, selective venous sampling of androgen
Exogenous sex steroids (e.g., testosterone creams and estradiol spray or creams)	Suppressed	Absent LH response	Elevated testosterone in boys and estradiol in girls	Estrogen preparations cause feminization, while topical androgens cause virilization in both sexes	Clinical history explores use of exogenous sex steroids by caretakers and folk remedies. Monitor sex steroid hormone levels and clinical status after removal of inciting agent.

LH, luteinizing hormone; GDPP, gonadotropin-dependent precocious puberty; GnRH, gonadotropin-releasing hormone; MRI, magnetic resonance imaging; hCG: human chorionic gonadotropin; FSH, follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulfate; CT, computed tomography.

[a]If adrenal tumor tissue loses sulfokinase activity, DHEAS may not be elevated.

From Saenger P. Definition, etiology, and evaluation of precocious puberty. UpToDate Web site. http://www.uptodate.com/contents/definition-etiology-and-evaluation-of-precocious-puberty. Accessed December 17, 2013.

TABLE 23.6 Evaluation of Incomplete Precocious Puberty

Etiology	Gonadotropin Levels	LH Response After GnRH Stimulation	Sex Steroid Hormone Levels	Clinical Features	Additional Evaluation
Premature adrenarche	Prepubertal LH levels	No LH response	DHEAS values elevated for age (at Tanner 2 levels, i.e., >50 mcg/dL) 17-OHP and testosterone normal Early pubertal response to ACTH	No other signs of pubertal development; normal growth rate Gonads prepubertal Onset usually after 6 years of age Associated more frequently with brain injury, obesity, or children born SGA	Monitor for possible early progression to full puberty
Premature thelarche	Prepubertal LH levels	No LH response, normal FSH response	Prepubertal	No other signs of pubertal development; normal growth rate	Monitor for possible early progression to full puberty

LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone; DHEAS, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; SGA, small for gestational age; FSH, follicle-stimulating hormone.
From Saenger P. Definition, etiology, and evaluation of precocious puberty. UpToDate Web site. http://www.uptodate.com/contents/definition-etiology-and-evaluation-of-precocious-puberty. Accessed December 17, 2013.

may show presence of ovarian pathology or uterine maturation. Serum estradiol levels above 100 pg/mL may be associated with maturation of an ovarian cyst or an estrogen-producing tumor. The gold standard is measurement of gonadotropins after GnRH or GnRH–agonist stimulation. Patients with central precocity will exhibit a pubertal, LH-predominant response; however, patients with GnRH-independent precocious puberty (peripheral precocity) have a suppressed response to GnRH. In all cases of central precocious puberty, magnetic resonance imaging (MRI) of the brain is needed to determine if a tumor is present in the hypothalamus.[97]

Hamartomas of the tuber cinereum are the most frequent benign tumors that cause GnRH-dependent precocious puberty. Other lesions such as hydrocephalus, trauma, brain cysts, central nervous system (CNS) inflammatory disease, and congenital midline defects of the CNS are also associated with GnRH-dependent precocious puberty. Irradiation of the brain may also cause GnRH-dependent precocious puberty and is often accompanied by growth hormone deficiency. Previous exposure to excess sex steroids (e.g., poorly controlled adrenal hyperplasia or McCune-Albright syndrome) and primary hypothyroidism that is severe and long-standing may also contribute to the development of central (GnRH dependent) precocious puberty.

Benign variants include isolated secondary sexual characteristics without increased growth velocity. These patients will have a prepubertal FSH-predominant response to GnRH stimulation. Isolated precocious thelarche refers to unilateral or bilateral breast development. Isolated precocious adrenarche is associated with pubic hair development, adult body odor, axillary hair, or mild acne. Isolated precocious menarche is vaginal bleeding without breast or pubic hair development, and without a vaginal lesion (tumor or foreign body) or trauma. Close follow-up is recommended because progression to full precocious puberty can occur.[98]

Peripheral or pseudoprecocious puberty is GnRH independent and the secondary sex characteristics that develop may be appropriate (isosexual) or inappropriate (contrasexual), for example, virilization in a girl. In these cases, FSH and LH are suppressed and do not respond to GnRH stimulation. Causes for girls include ovarian cysts, ovarian tumors (e.g., granulosa cell tumors, Sertoli-Leydig, pure Leydig, and gonadoblastoma tumors), exogenous estrogen, adrenal pathology, pituitary gonadotropin-secreting tumors, and McCune-Albright syndrome. McCune-Albright syndrome is rare and is composed of the triad of peripheral precocious puberty, café-au-lait spots, and fibrous dysplasia of bone. The most common manifestation is peripheral precocious puberty and the sequence of pubertal development may be abnormal. It is more common in girls than in boys and treatment depends on the sex of the child and clinical phenotype.

Incomplete precocious puberty is usually a variant of normal puberty. Radiologic confirmation should be sought to ensure there is not premature epiphysial maturation; if not, no other tests are usually required apart from monitoring every 6 months for development of true GnRH-dependent precocious puberty, which occurs in 14 to 20% of children.[99] Premature thelarche is a common presentation and is idiopathic; it may present around 2 years of age (or earlier) and either remit spontaneously or progress slowly or, alternatively, the second peak is at ages 6 to 8 years. It maybe unilateral or bilateral. Premature adrenarche is more common in girls, black females, and children with obesity and insulin resistance. It is a risk factor for polycystic ovary disease in girls and follow-up is recommended.

Delayed Puberty

Delayed puberty is defined as a failure to begin sexual maturation at an age that is two standard deviations

above the mean age of the onset of puberty within a specific population; in the United States, a girl who has not shown any pubertal development by age 13 years or achieved menarche by age 15 years should have medical evaluation.[100] Common causes for delayed puberty include constitutional delay, genetic defects, or hypothalamic–pituitary disorders. A careful history and physical examination are crucial, with a focus on family history (i.e., pubertal age of relatives or any genetic diseases); chronic medical conditions; and any prior surgery, radiation, or chemotherapy. Serum gonadotropin levels are useful in differentiating between hypogonadotropic hypogonadism as seen with low or normal serum LH and FSH levels thus reflecting a lack of GnRH versus hypergonadotropic hypogonadism with high levels of LH and FSH and reflective of gonadal failure or a defect in the gonadal cell receptors for LH and FSH. Hypergonadotropic hypogonadism is also referred to as primary hypogonadism and hypogonadotropic hypogonadism is secondary hypogonadism and may be caused by hypothalamic dysfunction, hypopituitarism, hypothyroidism, or hyperprolactinemia. (Table 23.7 lists the diverse potential causes of delayed puberty.) When menarchal delay occurs in the setting of normal pubertal development, a müllerian anomaly must be considered.

There is no single test to distinguish between cases of constitutional delay of puberty and other causes of delayed puberty. As such, a thorough history and physical is key in guiding the evaluation. Information about nutrition, prior illnesses or medications, and exercise habits is informative, as are the presence of known congenital malformations. Midline defects (e.g., cleft lip/palate, scoliosis) may indicate a congenital GnRH deficiency. Family history around pubertal development may be useful in determining there is simply constitutional delay as there does appear to be an autosomal dominant mode of inheritance for this.[101] An absent or abnormal sense of smell may indicate Kallmann syndrome.

In the physical exam, both the standing height and arm span should be measured. If the arm span exceeds height by more than 5 cm, this may indicate delayed epiphyseal closure due to hypogonadism. Tracking the height velocity is recommended in these cases.

An x-ray of the left hand and wrist may be ordered to evaluate bone age and may be repeated over time. Other imaging studies, for example, pelvic ultrasound or head MRI, should be ordered based on history and physical findings. Laboratory testing may include LH and FSH levels, prolactin levels, and TSH. GnRH stimulation testing is not recommended because there is considerable overlap between the causative groups of delayed puberty. Depending on findings in the history or physical exam, measurement of adrenal androgens or karyotype may be indicated as well.

If a specific disorder is identified, it should be addressed. In many cases, the initial therapeutic approach is expectant management or administration of exogenous gonadal steroids if the girl is older than 12 years of age. Therapy may continue until age-appropriate secondary sex characteristics are obtained or a growth spurt is induced without inducing premature epiphyseal closure as evidence by longitudinal monitoring of bone age every 6 months during therapy. For girls, this estrogen therapy is usually given at doses below those of hormone replacement dosages used in adults, that is, perhaps starting with a dose of conjugated estrogens of 0.3 mg/day or oral micronized estradiol of 0.25 mg/day or transdermal estradiol of 14 mcg/day. Progestins do not need to be used until there is substantial breast development as premature use of progestin therapy may compromise ultimate breast growth. The use of growth hormone is controversial and beyond the scope of this chapter.

TABLE 23.7 Causes of Delayed Puberty

Primary hypogonadism—High FSH and LH

Congenital
- Chromosomal abnormalities (Turner syndrome, 45,XO; Klinefelter syndrome, 47,XXY)
- Anorchia (vanishing testis)

Acquired
- Autoimmune or postinfectious
- Following trauma or surgery
- Chemotherapy, radiation therapy

Secondary hypogonadism—Low to normal FSH and LH

Acquired
- Tumors
  - Benign tumors and cysts
  - Craniopharyngiomas
  - Germinomas, meningiomas, gliomas, astrocytomas
- "Functional" gonadotropin deficiency
  - Constitutional delay of puberty
  - Chronic systemic disease
  - Acute illness
  - Malnutrition
  - Hypothyroidism, hyperprolactinemia, diabetes mellitus, Cushing's disease
  - Anorexia nervosa, bulimia
- Infiltrative diseases
  - Hemochromatosis
  - Granulomatous diseases
  - Histiocytosis
- Head trauma
- Pituitary apoplexy
- Drugs—marijuana

Congenital
- Isolated GnRH deficiency
  - Without anosmia
  - Kallmann syndrome
  - Associated with adrenal hypoplasia congenita
- GnRH deficiency associated with mental retardation/obesity
  - Laurence-Moon-Biedl syndrome
  - Prader-Willi syndrome
- Idiopathic forms of multiple anterior pituitary hormone deficiencies
- Congenital malformations often associated with craniofacial anomalies

FSH, follicle-stimulating hormone; LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone.
From Crowley WF Jr, Pitteloud N. Diagnosis and treatment of delayed puberty. UpToDate Web site. http://www.uptodate.com/contents/diagnosis-and-treatment-of-delayed-puberty. Accessed December 17, 2013.

Polycystic Ovary Syndrome

Because several features of polycystic ovary syndrome (PCOS) may overlap with normal adolescent development, there are no formal diagnostic criteria for adolescents with PCOS. In adults, PCOS is defined by the presence of menstrual irregularities due to chronic anovulation in combination with hyperandrogenism and/or polycystic-appearing ovaries on ultrasound. It has been suggested that a definitive diagnosis of PCOS in this population should require all three of the following modified Rotterdam criteria: hyperandrogenemia, oligomenorrhea for at least 2 years, and polycystic ovaries more than 10 mL on ultrasound.[102] Some prefer to use the National Institutes of Health (NIH) criteria, which would require hyperandrogenism and an abnormal menstrual pattern. Chronic anovulation and menstrual irregularities are common in adolescence; up to 85% of all cycles are anovulatory in the first year after menarche. Even 4 years after menarche, only 56% of the cycles are ovulatory.[103] The relationship between adolescent anovulation and the development of PCOS is unclear. There is no consensus about the applicability of adult ovarian criteria to adolescents and many healthy girls will be found to have multifollicular ovaries as a stage of development. The natural history of PCOS in adolescents is not well documented, although it would seem that once hyperandrogenemia develops, it seldom regresses.

There are associated metabolic abnormalities, including obesity, insulin resistance, and dyslipidemia. It has been shown that up to 30% of teenage girls with PCOS already have impaired glucose tolerance.[104] Although there are no published guidelines for the treatment of PCOS in adolescents, lifestyle changes such as healthy food choices, portion control, and daily exercise must remain first and foremost.[105] Use of combination oral contraceptives can induce cyclical bleeding and reduce some of the signs of androgen excess (see Chapter 3: Hyperandrogenism).

ANATOMIC ABNORMALITIES

Prior to birth, male and female external genitalia pass through a phenotypically indifferent stage during which it is impossible to differentiate between the two sexes. The presence of the Y chromosome will direct testicular development, through a switch gene present on its short arm, called the SRY gene.[106] This gene, along with other testes determining factors (TDFs), will guide the differentiation of the undifferentiated gonad into testicular tissue which produces testosterone. Under the influence of testosterone, the external genitalia assume a masculine appearance, but the derivatives are homologous between males and females. These homologies include (a) the clitoris and penis, derived from the genital tubercle; (b) the labia majora and scrotum, derived from the genital swellings that fuse in the male; and (c) the labia minora and penile urethra, derived from the urethral folds that fuse in the male. In the absence of TDFs and anti-müllerian hormone (AMH), which is produced by testes, ovarian tissue develops, and the paramesonephric female system forms. This includes the uterine tube, uterus, cervix, and upper portion of the vagina. Female external genitalia develop, including the clitoris, labia, and lower portion of the vagina. Any abnormality that affects the process of sexual differentiation may lead to conditions where the phenotype and genotype are discordant, or the external genitalia are ambiguous at birth. Disorder of sex development (DSD) has become the consensus umbrella term for describing any congenital condition in which the development of chromosomal, gonadal, or anatomical sex is atypical.[107] The American Society for Reproductive Medicine has classified müllerian anomalies of the female reproductive tract into sex categories (see Table 23.8).

The hymen is originally a solid membrane that undergoes apoptosis during the fetal period to become patent. Abnormalities in this process can result in variations including imperforate hymen (no opening), microperforate hymen (a single small opening), cribriform hymen (multiple small openings), and septate hymen (a residual band, usually in the anteroposterior diameter).[108] It is important to realize that hymens change with age and weight. Infant girls have estrogenized hymens and may have a prominent ridge at 6 o'clock. The hymen of prepubertal girls is unestrogenized, thin, and may have a multitude of appearances (Figs. 23.5 and 23.6). The hymen is of urogenital origin in contrast to the uterus and vagina, which are of müllerian origin. Therefore, the concomitant renal malformations seen with müllerian anomalies are not associated with hymenal anomalies.

Imperforate hymen is one of the most common obstructive lesions of the female genital tract (Fig. 23.12). At birth, infants may have a bulging introitus due to a mucocolpos. If this is left alone, the mucus will be resorbed but at menarche, the adolescent may present with cyclic abdominal or pelvic pain, back pain, and/or difficulty with defecation or urination and a hematocolpos. Treatment of the imperforate hymen is ideally done when the tissue has been stimulated with estrogen: newborn, postpubertal, or premenarcheally. Treatment is surgical repair with elliptical excision of the membrane close to the hymenal ring and evacuation of the obstructed materials. This is followed by suturing the vaginal mucosa to the hymenal ring using fine suture materials.

Incomplete opening or fenestration of the hymen may lead to difficulty inserting tampons, vaginal creams, or sexual intercourse. Patients may also experience premenstrual spotting or foul-smelling discharge due to the partial obstruction these cause. Treatment is surgical and similar to that described for imperforate hymenal repair.

TABLE 23.8 Classification of Müllerian Duct Anomalies

Classification	Clinical Finding	Description
I (5–10% MDAs)	Segmental or complete agenesis or hypoplasia	Agenesis and hypoplasia may involve the vagina, cervix, fundus, tubes, or any combination of these structures. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is the most common example in this category.
II (10–20% MDAs)	Unicornuate uterus with or without a rudimentary horn	When an associated horn is present, this class is subdivided into communicating (continuity with the main uterine cavity is evident) and noncommunicating (no continuity with the main uterine cavity). The noncommunicating type is further subdivided on the basis of whether an endometrial cavity is present in the rudimentary horn. These malformations have previously been classified under asymmetric lateral fusion defects. The clinical significance of this classification is that they are invariably accompanied by ipsilateral renal and ureter agenesis.
III (5–20% MDAs)	Didelphys uterus	Complete or partial duplication of the vagina, cervix, and uterus characterizes this anomaly.
IV (10% MDAs)	Complete or partial bicornuate uterus	Complete bicornuate uterus is characterized by a uterine septum that extends from the fundus to the cervical os. The partial bicornuate uterus demonstrates a septum, which is located at the fundus. In both variants, the vagina and cervix each have a single chamber.
V (55% MDAs)	Complete or partial septate uterus	A complete or partial midline septum is present within a single uterus.
VI (unknown % MDAs)	Arcuate uterus	A small septate indentation is present at the fundus.
VII	DES-related abnormalities	A T-shaped uterine cavity with or without dilated horns is evident.

MDAs, müllerian duct anomalies; DES, diethylstilbestrol.
The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, müllerian anomalies and intrauterine adhesions. *Fertil Steril.* 1988;49(6):944–955.

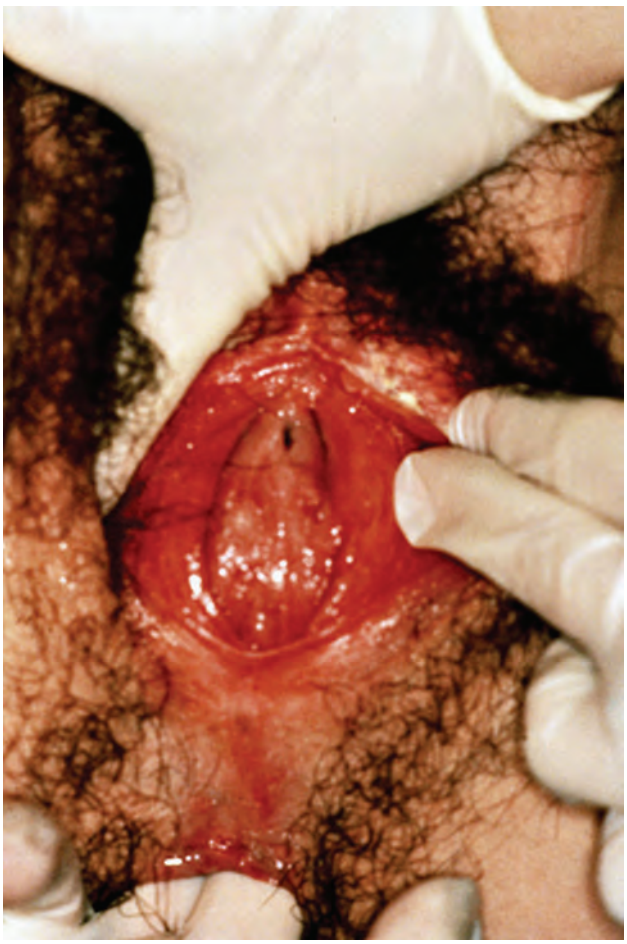

FIGURE 23.12 Imperforate hymen. (Reproduced from Emans SJ, Laufer MR, eds. *Pediatric and Adolescent Gynecology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2012, with permission. Copyright © 2012 Lippincott Williams & Wilkins.)

A transverse vaginal septum results from failure of fusion and/or canalization of the urogenital sinus and müllerian ducts. Septa may be located at various levels within the vagina, although the majority is in the mid- to upper portions of the vagina. They are usually less than 1-cm thick and may contain perforations. They may present as mucocolpos, hematocolpos, or pyohematocolpos and a mass may be noted on examination. MRI or ultrasound may help locate the placement of the septum and distinguish between a high septum and congenital absence of the cervix. Repair is surgical; for thick septums, it is advisable to have a surgeon with experience perform the procedure.

Longitudinal vaginal septa are often associated with uterine abnormalities and the septum may be partial or incomplete. Patients may be asymptomatic or report difficulty with placing tampons, bleeding despite the use of tampons, or dyspareunia. Treatment is surgical excision.

An obstructed hemivagina is often associated with ipsilateral renal agenesis, may present with pain or pus, and the diagnosis is usually made with history and physical examination combined with imaging. Treatment is surgical.

Agenesis of the lower vagina may present with primary amenorrhea and cyclic pelvic pain. There is normal development of the ovaries, uterus, cervix, and lower vagina and their presence may be confirmed on imaging. Treatment is surgical.

Defects of the müllerian system result from agenesis, lateral fusion defects, or vertical fusion defects. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is the manifestation of agenesis. Müllerian agenesis, commonly referred to as Mayer-Rokitansky-Küster-Hauser syndrome,

frequently presents as primary amenorrhea. There is complete agenesis of the vagina and variable development ranging from partial to complete agenesis of the cervix, uterus, and proximal fallopian tubes. There is normal ovarian development and normal secondary sexual characteristics. Patients may have normal hymenal development and often a 1- to 2-cm vaginal dimple. Frequently, there are extragenital anomalies as well. About 25 to 50% of these patients have urologic abnormalities (unilateral renal agenesis, pelvic kidneys, or abnormalities of the collecting system) and 10 to 15% have skeletal abnormalities that involve the spine, ribs, or extremities.[109] Less commonly, there may be abnormalities of the heart, hand(s), hernias, cleft palate, or even deafness. Evaluation should include assessment of the kidneys, confirm the presence of ovaries, and the absence of a uterus. Creation of a neovagina can be achieved through perineal dilation or by operative procedures (i.e., laparoscopic Vecchietti procedure); detailed discussion of these options is beyond the scope of this chapter.

Lateral fusion defects may result in uterine septa, unicornuate uterus, bicornuate uterus, or uterine didelphys. The extent of uterine septa varies from partial to complete. A unicornuate uterus is the result of complete development of only one of the müllerian ducts, with incomplete or failed development of the contralateral side, often associated with renal agenesis. Complete failure of fusion of the two müllerian ducts results in duplication of the cervix and uterus. Patients with uterine duplication often have a concurrent longitudinal vaginal septum, which can present with bleeding despite use of a single tampon (two are needed—one for each hemivagina) or dyspareunia.[110] This septum can be surgically resected. The presence of a functional uterine corpus with cervical agenesis is a rare anomaly. At the present time, most experts recommend a hysterectomy for patients with functioning endometrium and cervical agenesis.[111] Without surgery, these patients will develop recurrent hematometra causing a pelvic mass and cyclic pain.

The most common müllerian anomaly consists of two uterine horns (bicornuate uterus). Complications of this defect include a higher incidence of spontaneous abortion and abnormal fetal presentations. In some cases, part of the uterus has a blind end (rudimentary horn), leading to problems with menstruation and abdominal pain. Removal of a rudimentary horn is indicated prior to pregnancy regardless of horn type.[112]

Uterine didelphys is usually limited to duplication of the uterus and cervix (bicollis), although duplication of the vulva, bladder, urethra, vagina, and anus may occur. About 15 to 20% of patients with uterus didelphys will have other unilateral anomalies such as an obstructed hemivagina or ipsilateral renal agenesis.[113] Most of these anomalies (65%) are on the right.

Vertical fusion defects of the müllerian system may result in vaginal septum (previously discussed) or cervical agenesis or dysgenesis. Symptomatology is determined by the extent of obstruction accompanying the defect(s).

OTHER DISORDERS OF SEX DEVELOPMENT

Turner syndrome is an important cause of primary amenorrhea and short stature in girls and is caused by loss of all or part of an X chromosome. (Growth hormone levels are normal in these cases despite the short stature.) Turner syndrome is the most common sex chromosome abnormality. In most two-thirds of cases, the maternal X is retained and in the remaining third, it is the paternal X chromosome. Over half of Turner patients exhibit mosaicism (45X/46XX). In cases of Turner syndrome where there is a Y chromosome, for example, a mosaic of 45X/46XY, there is an increased risk for gonadoblastoma. In these cases, prophylactic removal of the gonads is indicated, even if it appears to be a streak gonad. Hysterectomy is not routinely indicated as assisted reproductive technologies have enabled some women with Turner syndrome to become pregnant. Women with no Y chromosome do not have to have their gonads removed, even streak gonads.

Neonates with Turners syndrome may have congenital lymphedema of the hands and feet or two or more dysmorphic features such as webbed neck, nail dysplasia, high palate, and short fourth metacarpal. There are specific growth curves for this disorder. As women with Turner syndrome get older, they may develop hearing loss, hypothyroidism, and liver function abnormalities.[114–116] They may also develop autoimmune disease(s) such as autoimmune thyroiditis.[117] Renal anomalies are common in women with Turner syndrome and there is an increased risk of cardiovascular malformations and hypertension as well. Aortic dissection or rupture is increasingly recognized as a cause of death associated with Turner syndrome.[118]

Most women with Turner syndrome have no pubertal development, but some may develop normally and then develop secondary amenorrhea. Some may even have no morphologic defects and be of normal stature. Turner syndrome is the most common cause of premature ovarian failure. The ovaries are typically streak-like in appearance and may have no or only a few atretic follicles. For those patients with short stature, the use of recombinant human growth hormone is recommended in order to achieve maximal final height. Women with Turner syndrome require estrogen and progestin replacement therapy starting around the age of 12 years to permit normal pubertal development until the expected age of menopause. Doses of estrogen should be sufficient to prevent the long-term effects of hypoestrogenism such as osteoporosis.

Complete gonadal dysgenesis or XY gonadal dysgenesis (formerly known as Swyer syndrome) occurs when testicular development is abnormal in a genetic XY individual.

It is thought to be caused by a mutation of the SRY gene in 15 to 20% of affected patients. Most cases represent new mutations. The gonads produce no hormones in utero, postnatally, or in puberty. As a result, the external genitalia are female, and the lack of AMH secretion leads to normal development of the uterus, fallopian tubes, and vagina. It is recommended that gonadectomy be performed as soon as possible because these dysgenetic gonads have an increased risk of becoming malignant.[119,120] A typical presentation is a tall adolescent with primary amenorrhea and delayed puberty. Typically, people with complete gonadal dysgenesis are raised as female and begin hormone replacement therapy with estrogen and progesterone to induce menstruation and develop female secondary sex characteristics. In some patients, pregnancy may be achieved with assisted reproductive technologies.

Disorders in androgen synthesis or action are another cause of DSD. Congenital adrenal hyperplasia is the most common cause of ambiguous genitalia (accounting for more than 90% of cases), and salt-wasting forms may lead to rapid dehydration and fluid and electrolyte imbalance. Delay of diagnosis and treatment of congenital adrenal hyperplasia may be life-threatening. A deficiency in the enzyme 5-alpha-reductase results in a child born with female or mildly ambiguous genitalia who then goes on to become quite virilized at puberty. Complete androgen insensitivity syndrome (CAIS), caused by a defect in the androgen receptor, presents as primary amenorrhea in a 46XY individual with normal breast development and scanty pubic and axillary hair growth. The external genitalia are female; however, the uterus is absent and the vagina is blind ending. Leaving testes in situ until after puberty allows for breast development to happen naturally, but due to the presence of a Y chromosome, there is a risk for gonadoblastoma formation, so a gonadectomy must ultimately be performed. Once this has been done, these patients need to remain on long-term estrogen replacement. If the androgen receptor retains some activity, incomplete virilization occurs; this is known as partial androgen insensitivity syndrome (PAIS).

Parents of children with ambiguous genitalia benefit from counseling regarding the multifactorial nature of gender identity and multidisciplinary approach to the medical, surgical, and psychosocial management of these special patients. The need for and timing of feminizing genital surgery is currently an issue of debate. Until recently, the accepted practice was to perform genitoplasty in infancy. However, more current studies reveal the possibility that clitoral reduction surgery affects its sensitivity.[112] Furthermore, surgery performed in childhood may require revisions in adolescence due to postsurgical scarring. Whenever an adolescent presents with amenorrhea or cyclic pain, menstrual outflow obstruction should be considered, and examination of the external genitalia is necessary to document a patent outflow tract. The uterus is formed by fusion of the lower portions of the paramesonephric (müllerian) ducts. The vagina is formed by fusion of the paramesonephric ducts and the urogenital sinus. MRI is the most sensitive and specific imaging technique used for evaluating müllerian anomalies. Ultrasound can be a good initial screening tool; however, young children cannot be examined transvaginally. Thus, the transabdominal images obtained are highly dependent on the operator, presence of a full bladder, and the amount of abdominal fat between the ultrasound probe and the pelvic organs. Whenever a müllerian anomaly is present, evaluation of the kidneys should also be performed as renal anomalies are commonly associated with genital anomalies. Laparoscopy remains the gold standard for the evaluation of uterine anatomy, as vaginoscopy (or in an adolescent, thorough speculum examination) is for the evaluation of vagina and cervix.[121]

GYNECOLOGIC EMERGENCIES

Evaluation of Genital Trauma

Accidental injuries resulting in perineal trauma are fairly common, especially in the warmer climates when children are lightly dressed. Straddle injuries occur when a child straddles an object as he or she falls on to it. Straddle injuries are often seen with bike riding, playing on monkey bars, entering or exiting swimming pools, and climbing activities. Straddle injuries are normally unilateral and superficial and involve the anterior portion of the genitalia. Straddle injuries are classified as penetrating or nonpenetrating; penetrating injuries are much more serious and may be extensive. These types of injuries may be associated with injury to the urethra, bladder, peritoneum, or rectum. Important in the evaluation of any type of genital trauma is excluding the possibility of sexual abuse. When obtaining a history, the physician should evaluate the injury for compatibility with the patient's (or eyewitness's) story in order to confirm nonsexual trauma.

Trauma to the vulva may result in a vulvar hematoma or lacerations with subsequent vaginal bleeding. Vulvar hematomas and vulvar or vaginal lacerations are the most common types of straddle injuries seen in girls. The majority of vulvar hematomas does not need any special treatment and will resolve spontaneously. Treatment with ice is recommended for the first 12 to 24 hours after injury. Small vulvar hematomas can often be managed conservatively with the use of ice and observation, as long as the hematoma is not expanding. If the patient has a larger vulvar hematoma and is unable to void, one should place an indwelling urinary catheter and continue bladder drainage until the swelling resolves. Surgical evacuation of a large or expanding hematoma will reduce pain; hasten recovery; and prevent necrosis, tissue loss, and secondary infection.[6,122]

Most injuries are minor lacerations or abrasions of the labia minora and posterior fourchette, accompanied by bruising of the labia majora and mons.[122] If possible,

vulvar lacerations should be allowed to heal by secondary intent, particularly, if they are near the vestibule.

Vaginal injuries result from penetrating trauma. Objects that pierce the perineum may also cause direct vaginal injury. Most vaginal lacerations are superficial but if they are actively bleeding, may require surgical repair under general anesthesia.

Determination of the extent of the injury and deciding whether surgical repair is needed frequently necessitates an examination under anesthesia, including examinations to evaluate the integrity of the bladder and bowel. Indications for examination under anesthesia include an inability to void or concern about urethral integrity, ongoing genital bleeding requiring suture or hemostasis, suspected anal sphincter injury, and inability to fully assess the extent of the injury due to the child's discomfort or inability to cooperate for a comprehensive examination.[6,122] In the case of a penetrating injury or if hymenal injury cannot be excluded, care must be taken to ensure that the peritoneal cavity was not penetrated. If the rectum or peritoneal cavities are entered, an exploratory laparotomy or laparoscopy should be performed to determine the full extent of injuries and to initiate repairs.[6,122]

Sexual Abuse

The evaluation of a child for possible sexual abuse is a difficult and complicated task involving a complete history by a trained counselor as well as a medical evaluation. It is important for all clinician's as patient advocates to be able to recognize or suspect sexual abuse. Sexual assault is the attempted sexual touching of another without their consent and includes sexual intercourse, sodomy, and fondling, whether the victim is clothed or not. Sexual abuse may also occur with acts of exhibitionism, voyeurism, or involving the child in pornography.[123] Sexual play occurs without coercion and the children are of similar ages (no more than 4 years apart either chronologically or developmentally).[124] Sexual play is normal behavior.

Sexual abuse occurs primarily in the prepubertal years and girls are more likely to be sexually abused than boys. Boys are less likely to report sexual abuse. Most perpetrators are male and are often trusted acquaintances of the family. Sexual abuse of children occurs in all social, cultural, and economic backgrounds.

Children who are victims of sexual assault may present with a wide variety of complaints which may, or may not, be related to the abuse. These children may attempt to perpetrate sexual abuse on other children, act out explicit sexual acts, demonstrate inappropriate knowledge of sexual activities, or exhibit inappropriate play behaviors, for example, asking adults to touch their genitals or attempting to touch the genitals of adults.

The evaluation of possible sexual abuse includes a history and physical examination and may include collection of forensic evidence. It should seek to identify any injuries or conditions that need treatment, screen for and/or identify STIs, evaluate for and possibly reduce the risk of unwanted pregnancy, and document the findings that may be of potential forensic value. When possible, the evaluation should be done by an experienced child abuse team and are best done in the nonemergent setting, although this may not be possible if the abuse occurred in the last 72 hours, there are injuries present, there is obvious forensic evidence on the victim's body or clothes that need to be collected, there is fear of continued abuse or reprisal, or the victim reports suicidal or homicidal ideation.

The history is critically important as many times physical findings are not present. If possible, verbatim documentation of questions and answers is quite helpful. The history should include current and past medical problems as well as social and family histories. A review of systems should reflect if there are any changes in bowel or bladder habits, sleep changes, and/or behavioral changes. If possible, the history should be obtained by an experienced professional.

The physical exam should include inspection of the mouth, breasts, genitals, inner thighs, perineal region, buttocks, and anus. A good light source is essential. Colposcopy may help with its magnification in identifying subtle lacerations or tears and its photographic capabilities, but it is not essential. An ultraviolet or Wood's lamp may detect semen within several hours of the abuse but urine and fluids with oil will also fluoresce with a Wood's lamp.

The genital exam should include close inspection of the labia majora, labia minora, introitus, hymen, and anus for any evidence of erythema, lacerations, abrasions, tears, or lesions. Vaginal discharge should be evaluated for STIs. Findings of sexual abuse are often subtle or absent. In children with a history of vaginal or anal penetration, abnormal physical findings may be present only 15 to 20% of the time.[125] If a child presents with an injury to the vulva or perineum without a reasonable history to explain the injury, abuse should always be considered. Other suspicious findings include acute or healed lacerations of the hymen or posterior fourchette, hymenal transections to the base, and perirectal scarring.

Clinicians need to be cautious, however, about making judgments about abnormalities in children being evaluated for sexual abuse. The transverse width of the hymenal canal may be measured but there is no width that is diagnostic of sexual abuse. It varies with the type of hymen, method of examination and position of the child during the exam, and the degree of relaxation and cooperation of the child. It increases with the child's age and weight.[126] A narrow hymenal ring is not diagnostic of sexual abuse; in one study, 22% of nonabused children were found to have a hymenal rim measuring only 1 to 2 mm.[127] A complete transaction of hymenal tissue between 3 and 9 o'clock is very suspicious for trauma—accidental or sexual—but is not diagnostic of the cause in

and of itself. Notches in the posterior part of the hymen may occur naturally and it is not possible to determine if they represent a site of healed trauma or normal variation based on appearance or presence alone. It is important that any hymenal variations noted be described with anatomically descriptive terms and not with adjectives such as "virginal" or "nonvirginal" nor with words denoting an action known to be fact, for example, "ruptured."

Nonspecific findings of sexual abuse can include vulvar erythema, vulvovaginitis, and excoriations. Rapid healing of these injuries has been documented, often within several days.[128] For this reason, it is imperative that a child or adolescent be examined as soon as possible when there is a suspicion of a possible sexual assault. Unfortunately, the exam is often completely normal even in cases of known penetration. In a study of 2384 children referred for possible sexual abuse, 96.3% had a normal examination; furthermore, the incidence of abnormal medical findings was only 5.5%, even in children who had a history of anal or vaginal penetration.[129] Cultures and serum should be obtained for comprehensive STI screening if the child has symptoms, if there is genital trauma, or with any history of penetration. It should be noted that preadolescent children can be exposed to sexually transmitted organisms through several routes that may or may not include sexual abuse. Modes of transmission in nonabuse cases include in-utero and perinatal exposure from mothers with an STI and nonsexual, genital hygiene care.[130]

Ovarian Torsion and Cyst Rupture

As in adult women, torsion or cyst rupture must be considered in all girls with acute abdominal or pelvic pain found to have an ovarian cyst or tumor. In children, adnexal torsion may occur with normal-sized tubes and ovaries.[131] We advocate a conservative surgical approach, with prompt evaluation and early intervention if adnexal torsion is suspected. If adnexal torsion is found in a child or teen during an emergency laparoscopy, it is critical to attempt to detorse the adnexa, observe for signs of reperfusion, and salvage the ovary/tube when possible.

The ovary is continually maturing follicles, and the presence of follicles (small ovarian cysts) on a sonographic study indicates functioning healthy ovaries. Ovarian cysts are normal findings and will resolve spontaneously over the course of a follicle lifespan. Large cysts (greater than 4 cm) can be painful and are a risk for torsion. Simple cysts are generally benign and can be managed conservatively by observation. Hemorrhagic corpus lutea are also common and may be painful but usually have a characteristic appearance on sonographic examination and will resolve with time. Surgical intervention should be discouraged for evaluation of physiologic follicles and corpora lutea, and if they are found on a laparoscopic examination for some other indication, they should be left alone. However, rupture of a corpus luteum cyst may result in hemoperitoneum and require surgical intervention to control the bleeding or manage pain. Large symptomatic cysts may be drained, but the cyst capsule should be excised to prevent recurrence and provide a histologic diagnosis. Under no circumstance is it defensible to remove a young woman's ovary for a physiologic cyst or corpus luteum.

OVARIAN NEOPLASMS

Ovarian tumors may be asymptomatic or may cause pain due to size, leakage, or torsion. They may be found incidentally or in the course of evaluation for nausea, vomiting, weight loss, abdominal distention, precocious puberty, or hirsutism. The most common ovarian neoplasm in children and adolescents is the mature cystic teratoma (dermoid cyst). Most are benign and contain mature tissue of ectodermal, mesodermal, or endodermal origin. The mature dermoid cyst may contain skin, hair, sebaceous glands, teeth, cartilage, and bone. Calcification on an abdominal radiograph is a hallmark of a benign teratoma. Although they are usually benign, because recurrence is likely, teratomas should be carefully resected while preserving as much normal ovarian tissue as possible.

In general, ovarian cancer is a rare disease in children, with only 2% of all ovarian cancers diagnosed in patients younger than the age of 25 years. The published National Cancer Institute incidence rates are less than 0.8/100,000 at ages 0 to 14 years and 1.5/100,000 at ages 15 to 19 years. Germ cell tumors are the most common source of ovarian cancer in this age group. These malignant cells originate from primordial germ cells, which lead to heterogeneous tumor types including dysgerminomas, immature teratomas, endodermal sinus tumors, embryonal carcinomas, mixed cell neoplasms, and gonadoblastomas. Immature teratomas and endodermal sinus tumors are more aggressive malignancies than dysgerminomas and often occur in younger girls, younger than 10 years of age. Immature teratoma of the ovary is an uncommon tumor, comprising less than 1% of ovarian teratomas. Sex-cord stromal tumors are more common among adolescents. Tumor markers are helpful for following the patients' response to therapy but should not be used for screening purposes. A pediatric oncologist or gynecologic oncologist should be involved in the management of children and adolescents with ovarian malignancies.

CHRONIC PELVIC PAIN

The diagnosis and management of chronic pelvic pain in adolescents can be frustrating for both patients and physicians. A detailed history should be obtained, including a complete menstrual and sexual history, and identification of any associated symptoms such as gastrointestinal ailments, urinary complaints, and stress at school or home. In evaluating an adolescent patient with chronic

pelvic pain, abdominal wall assessment for signs of muscle injury and trigger points is helpful because this indicates that physical therapy is likely to be useful in the management of pain symptoms. Initial testing should include a urine pregnancy test, PCR for gonorrhea and chlamydia, and a urinalysis/urine culture. A pelvic ultrasound may be helpful to document a uterine anomaly, ovarian lesion, or other pelvic pathology.[132] Also useful is symptom tracking using a menstrual calendar. Endometriosis should be considered in any adolescent girl with chronic pelvic pain that is refractory to nonsteroidal anti-inflammatory drugs (NSAIDs) or OCPs.[133] Other etiologies that should be considered include musculoskeletal pain and interstitial cystitis (IC).[134]

Endometriosis, defined by the presence of endometrial glands and stroma outside the uterus (typically in the pelvis), has traditionally been thought to occur only rarely in adolescence. However, the incidence of endometriosis in adolescent girls undergoing laparoscopy for pelvic pain ranges from 25 to 67%.[135,136] Although the etiology of endometriosis remains an enigma, the theory of retrograde menstruation with implantation in the peritoneal cavity may be particularly important in adolescents with obstructive müllerian anomalies. Theoretically, once an obstructed anomaly is removed or relieved, the endometriosis may resolve. On laparoscopy, younger patients may have atypical findings of "red flame-like" or clear vesicular lesions. Endometriosis has been described in premenarchal girls,[137,138] and has also been documented to occur within 1 month of menarche.[139] Endometriomas of the ovary and powder-burn or white lesions are more common in older patients who have a longer history of the disease process.[140]

The treatment for adolescents with suspected or diagnosed endometriosis has been adapted from adult cases. Medical management, including NSAIDs and hormonal therapy (continuous OCPs or progestins) is the initial approach in the adolescent patient. Laparoscopic diagnosis of pelvic endometriosis, with ablation or resection of lesions, should be reserved for the patient with persistent pain despite medical treatment. The goal of therapy is to treat the pain, cease progression of the disease, and preserve fertility.[141] GnRH agonists, which are routinely used to suppress the lesions in adults with endometriosis, should be reserved for adolescents who have failed the primary treatment regimens previously described. Although GnRH agonist therapy is known to have a negative effect on BMD, there is evidence supporting the effectiveness of add-back therapy (daily norethindrone acetate) in preventing bone loss in adolescents.[142] The use of GnRH suppression in adolescents is recommended for approximately 6 months followed by continuous OCP use.

CLINICAL NOTES

- A variety of gynecologic problems commonly occur in young girls, including vaginal discharge or bleeding and vulvar disorders. Gynecologic referrals also are made for abnormalities of pubertal development or congenital anomalies.
- The genital examination for prepubertal girls requires a gentle, patient approach to minimize fear or embarrassment. Assessment of the prepubertal child usually can be accomplished in the office setting. Forcible restraint is never indicated and sedation is rarely necessary.
- A speculum examination should not be attempted in the office examination of a prepubertal child.
- Obstetrician–gynecologists should be familiar with pubertal hormonal patterns and psychological and physical developmental stages. This will assist in the counseling, examination, and identification of ambiguous genitalia, precocious puberty, and other hormonal disorders in the prepubertal child.
- Vulvovaginitis is the most common gynecologic complaint in prepubertal children. Poor hygiene and chemical irritants are the most common causes of vulvovaginitis in the prepubertal child and it is usually improved by hygiene measures and education of the caregivers and child.
- Although oral contraceptives are a popular method of hormonal contraception, other LARC methods have higher efficacy (IUDs and implants) and greater adherence rates.
- Sexual abuse should be considered in the course of an evaluation for vaginitis, vaginal bleeding, or trauma. Findings suspicious of abuse include presence of STIs or sperm; lacerations of the vulva, posterior fourchette, or anus; and transections of the hymen. However, most sexually abused children will have normal findings on examination.
- A foreign body must be considered in children with persistent foul vaginal discharge or vaginal bleeding and an examination under anesthesia should be considered.
- Straddle injuries are the most common accidental genitourinary trauma and can result in ecchymosis or hematoma formation of the vulva but rarely result in penetrative or vaginal trauma.
- Anovulation due to immaturity of the HPO axis is the cause of dysfunctional uterine bleeding in most adolescents.
- Laparoscopic surgery is indicated in patients with pelvic pain refractory to medical treatment.

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CHAPTER 24

Care of Perimenopausal and Postmenopausal Women

Ann Honebrink and Kurt T. Barnhart

Average life expectancy at birth for women in the United States has increased from 48 in 1900 to 80.4 in 2005.[1] It is a relatively new phenomenon for women to spend a significant portion of their lives in the post reproductive state. As average life expectancy increases, so does the number of elderly Americans; by 2050, it is estimated that more than 20% of the population will be older than 65 years of age. In the United States, the most rapid growth is estimated to occur between 2010 and 2030, as the American "baby boomers" reach 65 years of age. Because women's life expectancy is longer than men's, the majority of this growing elderly population will be women.[2] The average age of a woman at menopause is 51 years, and more than 90% of women are postmenopausal by 55 years of age.[3] Many women are interested in information about how to best negotiate their post reproductive years and a large variety of literature is available on the topic in both the medical and lay press. As women spend more of their lives in the postmenopausal state, the changes associated with menopause are becoming better described and more fully understood. The continued expansion of this knowledge and the development and evaluation of lifestyle and screening recommendations as well as treatment options to optimize the health and well-being of this population is especially worthwhile given the expected continued growth of this population.

The menopausal transition and ensuing menopausal state has enormous health implications for a woman. Reproductive capabilities are most obviously affected, but menopause also has a potentially large impact on cardiovascular health, mood, musculoskeletal symptoms, bone mass and fracture risk, cancer risk, and cognitive function. Estrogen receptors are omnipresent in the human body. Separating the effects of menopause from those of the normal aging process can be a challenge for both patients and clinicians. This chapter reviews the important changes that accompany the menopausal transition and beyond, as well as the therapies and preventive strategies available for symptomatic relief and long-term disease prevention. As women spend more years in the postmenopausal state, this period in a woman's life becomes an opportunity to promote healthy behaviors and improve the adoption of appropriate preventive measures and screening techniques (Table 24.1).

Whether to "treat" menopause with replacement of reproductive hormones (estrogen and/or progesterone and/or testosterone) has been a subject of much study and controversy since synthetic estrogen became available in the mid-20th century. Common clinical recommendations have ranged from regarding menopause as an estrogen-deficiency disease that should be treated with estrogen replacement therapy to prevent the otherwise inevitable "living decay"[4] to treating symptoms only if absolutely necessary "for the shortest time with lowest dose possible"[5] and all points in between. Current thinking on this topic is also reviewed in this chapter.

DEFINITIONS

The language we use to describe the menopausal transition has been historically varied in both definition and context. Because this is a transition all women experience if they live long enough, our patients often have their own conceptions regarding this time in their lives. Having well-defined language to describe this period in a woman's life helps us to increase our patients' understanding of this life event and also gives us a descriptive context for communication of research findings and clinical experience. As more study has been done of the natural history of the menopausal period, the following terms have been developed and used in this chapter. Although other symptoms, especially vasomotor symptoms, often accompany the transition to menopause, these definitions rely on menstrual patterns since hallmark of menopause is the cessation of menses.

Menopausal Transition: Menopausal transition describes the time from the onset of variations in the menstrual cycle and a rise in follicle-stimulating hormone (FSH) levels until 12 completed months of amenorrhea. This transition may also be referred to as perimenopause or climacteric and is a process that may occur over many years.[6]

Menopause: Menopause is the permanent cessation of menses secondary to the follicular depletion; it is considered to have occurred following 12 consecutive months of amenorrhea. This can occur naturally or be induced by bilateral oophorectomy, radiation to

TABLE 24.1 Recommended Screening Tests and Immunizations in Healthy Menopausal Women

Screening Test	Age and Frequency	Purpose
Pap test	Every 3 years for low-risk women older than 30 years of age	Cervical cancer detection
Breast exam	Yearly by physician Monthly self-exam	Breast cancer detection
Mammogram	Every 1–2 years after age 40 years; yearly after age 50 years	Breast cancer detection
Digital rectal exam	Yearly after age 50 years	Colorectal cancer detection
Flexible sigmoidoscopy	Every 3–5 years after age 50 years	Colorectal cancer detection
Densitometry	Age 65 years if low risk At menopause if high risk	Osteopenia/osteoporosis detection
Lipid profile	Every 2 years after age 40 years	Cardiovascular risk assessment
Fasting glucose	Every 3 years after age 45 years	Diabetes detection
Sexually transmitted infections (STIs) and HIV testing	Yearly in high-risk patients	STIs and HIV detection
PPD skin testing	Yearly in high-risk patients	Tuberculosis detection
Immunizations		
Influenza vaccine	Yearly after age 50 years, or earlier if high risk	Influenza prevention
Pneumococcal vaccine	Once at age 65 years, or earlier if high risk	Pneumonia prevention
Tetanus-diphtheria vaccine	Every 10 years	Tetanus and diphtheria prevention

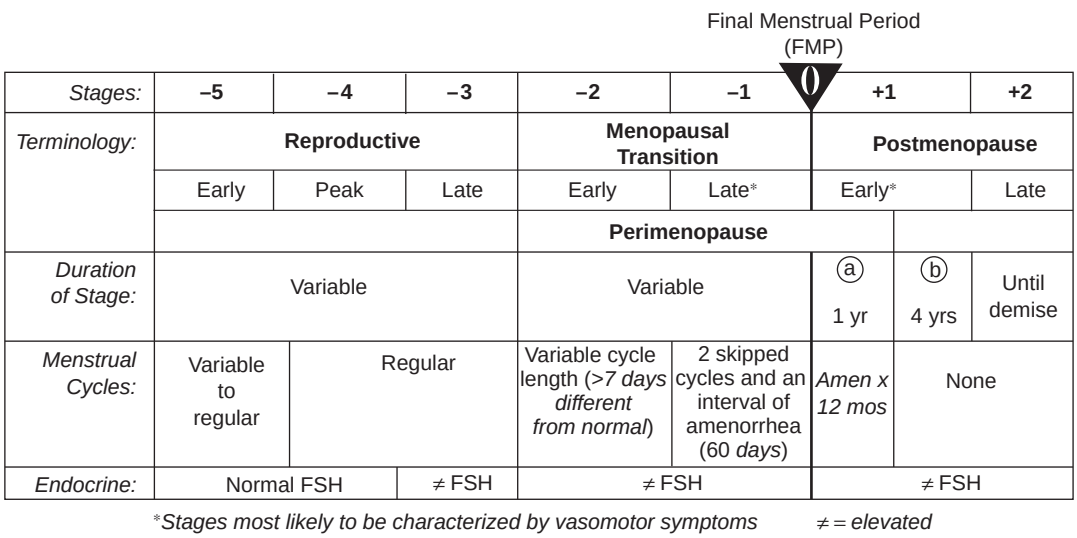
Adapted from American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. ACOG Committee Opinion No. 452: primary and preventive care: periodic assessments. *Obstet Gynecol.* 2009;114:1444–1451.

the ovaries, or by chemotherapy effects on ovarian follicular reserves.[6]

Postmenopause: Postmenopause is the remaining life period of the woman after 12 consecutive months of amenorrhea.[6]

NATURAL HISTORY OF MENOPAUSE

Several studies have been published describing the timing, duration, hormonal changes, and associated symptoms experienced by large populations of women passing thru this transition period.[7,7a] There is great variability in the age of onset and duration of the menopausal transition, but it appears that most women begin the transition at about age 47 and the median length from the onset of the transition to the final menstrual period (FMP) is 3.8 years.[3] Staging systems such as the Stages of Reproductive Aging Workshop (STRAW) classification (Fig. 24.1) have been proposed attempting to describe the factors associated with the usual progression



*Stages most likely to be characterized by vasomotor symptoms ≠ = elevated

FIGURE 24.1 STRAW staging system. (Reprinted from Fertil Steril 2001;76[5], with permission.)

through the menopausal transition and to help predict how soon the FMP will occur. An intermenstrual interval of greater than 60 days is both predictive of the FMP within 2 years[8,9] as well as current failure of ovulation.[10]

By definition, menopause is a diagnosis made in retrospect. The average age of permanent cessation of menstrual bleeding is 51.4 years.[3] Factors associated with an earlier age of menopause include poor nutritional status, family history, vegetarianism, and living at high altitudes. Women who currently smoke appear to experience menopause 1.8 years earlier than nonsmokers. Alcoholism has also been linked to delayed menopause.[11–17] While age at natural menopause is most likely influenced by genetic factors, and a number of genetic regions have been studied, as yet there is no clear understanding of which regions of the genome are involved with an individual's menopausal timing.[18]

ENDOCRINOLOGY OF THE MENOPAUSE TRANSITION

A woman is born with all the ovarian follicles she will ever develop; over time, these follicles become depleted. When the number of follicles drops very low, inhibin levels decrease and activin rises.[19] Negative feedback from the ovary to the pituitary diminishes, resulting in rising FSH levels.[20,21] The initial elevation in FSH is first detectable only in the early follicular phase. During the early menopausal transition, in response to the increased FSH stimulation, estradiol levels fluctuate widely and can actually be higher than average levels found in women younger than 35 years of age.[22,23] Estrogen levels do not begin a major decline until a year or so before menopause.[24] During perimenopause, FSH levels vary significantly across cycles.[25] Postmenopausal levels of FSH (>20 IU/L) may be seen despite the presence of menstrual bleeding, although luteinizing hormone (LH) levels remain in the normal range. Because of this variability of hormonal secretion during the menopausal transition, the diagnosis of perimenopause and menopause is not made based on laboratory studies but instead depends on the patient's individual symptoms and menstrual history. However, elevation in FSH in the early follicular phase has been associated with poor prognosis for future fertility and success of efforts at induction of ovulation.[26]

After menopause is completed, there is a 10- to 20-fold increase in FSH (>25 IU/L) and about a three-fold increase in LH (>30 IU/L).[27] Almost all postmenopausal production of estrogen is derived from the peripheral conversion of androgens.[28] Although reduced from earlier premenopausal levels, the ovary still secretes androstenedione and testosterone in the early postmenopausal years.[29] In the later postmenopausal years, circulating androgens are almost all derived from the adrenal gland.

This natural decline in estrogen is responsible for the various physiologic effects described in the following sections.

SYSTEMIC AND SYMPTOMATIC EFFECTS OF MENOPAUSE AND THE MENOPAUSE TRANSITION

Fertility

For many perimenopausal women, menstrual cycle length increases and anovulation becomes more prevalent, particularly in the 2- to 8-year period prior to menopause. During this time, there is an accelerated rate of loss of ovarian follicles until the supply is finally depleted.[30] Although these changes reflect increasing difficulty in achieving pregnancy, pregnancy can and does occur in perimenopausal women. Approximately 51% of pregnancies in this age group are unintended.[31] It therefore remains important during the menopausal transition to discuss the need for effective contraception with heterosexually active women not interested in becoming pregnant. For those interested in achieving pregnancy in this age group, FSH measurement on the third day of a naturally occurring menstrual cycle is predictive of ovarian reserve and response to ovulation induction. Elevated day 3 (or days 2 to 5) FSH levels are associated with a poor prognosis for success with ovulation induction.[32]

Menstrual Cyclicity and Abnormal Bleeding

During the reproductive years, normal menstrual cycles typically occur every 21 to 35 days. Variation in the timing, duration, and amount of menses signals the beginning of the menopausal transition. In perimenopause, a reduction in progesterone production during the luteal phase is common. This reduction coupled with normal or even increased levels of estrogen production leads to hormonal imbalances and may be responsible for the menorrhagia some patients report during perimenopause. In early perimenopause, cycle length may shorten by 2 to 7 days secondary to a shortened follicular phase.[33] As the perimenopause progresses, cycles becomes increasingly irregular. As menopause approaches, menstrual flow may become lighter, and episodes of spotting may become more prevalent.[23]

Therefore, "abnormal" bleeding is common during the transition through menopause. It most often occurs as a result of the fluctuating hormonal environment and anovulation. Failure to ovulate regularly causes periods of unopposed estrogen stimulation of the endometrium. Prolonged estrogen exposure leads

to proliferation, which can eventually lead to episodes of irregular and even heavy bleeding. Such unopposed estrogen stimulation also can increase the risk for hyperplasia and endometrial cancer. Heavy bleeding, however, has been shown to correlate less with anovulatory cycles and more with obesity and leiomyomata.[33] The need to evaluate heavier or more frequent bleeding commonly arises in the perimenopausal woman. After pregnancy, endocrine etiologies are ruled out, biopsy is performed. Office endometrial biopsy is generally well tolerated and has been shown to be more than 90% sensitive for detecting endometrial cancer.[34] Transvaginal ultrasound with or without saline infusion may be used to evaluate the endometrium. In postmenopausal women, endometrial sampling is recommended if the endometrial stripe is thicker than 4 mm.[35]

Office diagnostic hysteroscopy is also a tool for the evaluation of the endometrium and the uterine cavity. Premedication with misoprostol may facilitate ease of cervical dilatation when cervical stenosis limits endometrial evaluation with biopsy and/or hysteroscopy.[36] A dilatation and curettage (D&C) with hysteroscopy is recommended for women with postmenopausal bleeding when an office biopsy and/or hysteroscopy is not possible and endovaginal ultrasound does not provide reassurance. In perimenopausal women, endometrial evaluation via ultrasound is best performed immediately after completion of menses because endometrial thickness can vary with a normal menstrual cycle. Because of normal cyclic variations in endometrial thickness in perimenopausal women, the use of endometrial thickness for exclusion of endometrial pathology is of limited use prior to achievement of postmenopausal status.

In addition to excluding endometrial hyperplasia and cancer, endometrial biopsy provides a "snap shot" of hormonal influences on the endometrium and can be used as a guide to treatment recommendations for bothersome bleeding patterns. In addition, the external genitalia, vagina, and cervix should be thoroughly inspected and a Papanicolaou (or Pap) smear considered to exclude other causes of bleeding.[37] For a more thorough discussion of abnormal bleeding, see Chapter 2.

Once pathology has been excluded, anovulatory bleeding may be treated hormonally. Use of a traditional postmenopausal hormone therapy regimen (estrogen with progestin) in the perimenopausal woman is less likely to regulate bleeding patterns caused by anovulation and/or commonly concurrent adenomyosis or fibroids. Therefore, this approach is not recommended. Monthly progestational therapies in conjunction with an appropriate nonhormonal contraceptive method or a combination hormone contraceptive (e.g., oral contraceptives, the contraceptive patch, or vaginal contraceptive ring) are optimal therapies. If not contraindicated, combined hormonal contraception preparations regulate bleeding, relieve vasomotor symptoms, reduce ovarian cancer, and maximize bone density in women.[37] Depo-medroxyprogesterone acetate (MPA) has been used to control bleeding and also to provide contraception, but calcium intake needs to be maximized. The levonorgestrel containing intrauterine system (LNG-IUS) was approved in 2009 by the U.S. Food and Drug Administration (FDA) for treatment of heavy menstrual bleeding in women also desiring contraception. It is a safe and convenient option. There is little support in the literature for cyclic MPA administration during the menopausal transition, despite its popularity.[38]

Cessation of combined contraceptive therapy can occur at ages 50 to 51 years. Some authorities recommend tapering to combined contraceptive to decrease the symptoms from abrupt estrogen withdrawal. This can be done by tapering one pill per week or even cutting patches into halves or quarters. Heterosexually active patients wishing to avoid pregnancy should be advised to use "backup" method when discontinuing hormonal contraception until they have experienced several months of amenorrhea. The decision to initiate postmenopausal hormone therapy once menses have stopped should be individualized depending on symptoms, individual risk factors, and patient goals.

Vasomotor Symptoms

Vasomotor symptoms are the most characteristic symptom of the menopausal transition and can be very troubling to women. The sudden sensation of extreme heat in the upper body, particularly the face, neck, and chest is referred to as a "hot flush" or "hot flash." It is estimated that 15 to 63% of perimenopausal women experience hot flushes, with a higher percentage of women reporting vasomotor symptoms in the later part of the menopausal transition.[32,39–42] Although hot flashes are a common phenomenon for up to 80% of American women at some point during the menopausal transition,[43] they are more common in women with increased body mass, lower exercise levels, smokers, and women with a history of premenstrual dysphoric disorder or depression.[44] There is also wide ethnic variation in occurrence of vasomotor symptoms in different ethnic groups, ranging from reported 0% in Mayan women in Mexico to 80% of Dutch women.[45]

Hot flashes are related to the timing of the last menstrual period as menopausal symptoms are found to be most severe in the late perimenopausal and early postmenopausal stages. As vasomotor symptoms increase in severity, so do the severity of atypical complaints (e.g., tenseness, irritability, lack of self-confidence, headache, muscle or joint pain, tiredness on waking).[46] The severity and duration of hot flashes among perimenopausal women is highly variable, although they are usually more frequent and more severe at night and are more likely to occur prior to and during menstrual bleeding.[3] Hot flashes are not correlated or directly related to endogenous estrogen levels.

Usually, hot flashes last 6 months to 5 years with an average duration of 2 years after the FMP.[49] Some women report bothersome hot flashes for up to 15 years after menopause.[47,48] When estrogen therapy is discontinued, vasomotor symptoms frequently resume. When helping guide women through this transition time, it can be helpful to emphasize the time limited nature of vasomotor symptoms without treatment. In general, these symptoms are most severe and bothersome in the perimenopausal and immediate postmenopausal period months and become more tolerable as time after the FMP lengthens.[47] Although vasomotor symptoms can be bothersome to women, not all women find this phenomenon to be life limiting enough to require treatment. Sleep disturbance caused by night sweats can, however, affect mood and quality of life. Vasomotor symptoms also tend to be more severe in women who undergo more abrupt iatrogenically induced menopause secondary to premenopausal oophorectomy, radiation, or chemotherapy.[49]

The pathophysiology of hot flashes is not fully understood. Thermoregulation in humans depends on three major cooperating factors: the central nervous system, the body core and the peripheral vascular system.[50] With a decline in estrogen production, the thermoregulatory center in the brain becomes unstable, leading to an acute activation of the sympathetic nervous system and peripheral vasodilatation with subsequent sweating, which is often followed by a compensatory cooling mechanism and even shivering. Hot flashes may also be accompanied by an accelerated heart rate and feeling of anxiety.[51] While a very common symptom accompanying the menopausal transition, vasomotor symptoms can also occur in other conditions, such as diabetes or thyroid disease, pancreatic tumors, leukemias, pheochromocytoma, carcinoid syndrome, certain drugs, neurologic disorders, and in reaction to nitrites or sulfites.[52]

Therapeutic Options

Since the World Health Initiative study, many patients and practitioners have shied away from hormone replacement therapy (HRT). It is important to remember that it had a mean age of 63 years and that only 3.5% of women were 50 to 54 years old. Also, the risk of breast cancer did not increase in the combined estrogen-progestin group until the fourth year. Several well-designed studies have shown the efficacy of oral estrogen therapy over placebo in relief of vasomotor symptoms in women passing through the menopausal transition. Currently, short-term therapy with estrogen (2 to 3 years but not more than 5 years) is reasonable. Both frequency and severity of both night sweats and day time hot flashes are reduced by estrogen therapy. Multiple estrogen doses as well progesterone regimens have been shown to be effective.[53] Other studies have also demonstrated the effectiveness of transdermal[54] and higher dose transvaginal estrogens in for relief of vasomotor symptoms.[55] Relief of vasomotor symptoms is not immediate for all women. It may take up to 4 weeks before symptom relief occurs.[56]

There is some evidence that a combination of estrogen and androgen may alleviate symptoms in women with refractory vasomotor symptoms.[47] It appears that lower doses of estrogen are required when androgens are added.[57,58]

Progestins alone also appear to be an effective treatment for hot flushes. A 74% reduction in vasomotor symptoms has been demonstrated with doses of 10 to 20 mg/day of oral MPA (or 150 mg intramuscularly every 3 months), or 20 mg twice a day of oral megestrol acetate reduced symptoms in 85% of patients.[59,60] In addition, norethindrone and norethindrone acetate in doses between 1.2 and 5 mg have been shown to be effective in relieving hot flushes in younger women undergoing gonadotropin-releasing hormone (GnRH) agonist therapy.[61]

Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and gabapentin have shown some promise in treating vasomotor symptoms. Studies have compared these drugs favorably with placebo but have not shown the same level of effectiveness as estrogen therapy in the relief of hot flushes.[62,63] These drugs also have not been approved by the FDA for treatment of vasomotor symptoms. The mechanism of the effectiveness of SSRI/SNRIs remains unclear, but it is understood that serotonin receptors in the hypothalamus are involved in temperature regulation.[64] Based on double-blinded, randomized controlled trials, venlafaxine (Effexor XR) therapy for hot flashes can be started at a dose of 37.5 mg/day. The dose can be increased to 75 mg if needed but doses higher than 75 mg/day seem to have more toxicity but are not associated with greater efficacy.[65] A similar trial with fluoxetine (Prozac), 20 mg/day, also demonstrated a significant reduction in hot flashes, although its effect seemed more modest than that seen with venlafaxine.[66] Another more recent trial demonstrated the efficacy of paroxetine controlled release (Paxil) at doses of 12.5 mg/day or 25 mg/day.[67] Paroxetine should not be used in women taking tamoxifen because it decreases metabolism of tamoxifen to its active metabolite and may therefore decrease tamoxifen's effectiveness. Other new antidepressants such as escitalopram[68] and desvenlafaxine succinate[69] also have data to show they are more effective than placebo in the relief of hot flushes. Although generally well-tolerated drugs, side effects of SSRI and SNRIs include nausea, difficulty with sleep, and dry mouth. In addition, SSRIs may have sexual side effects with inhibition of orgasm. These drugs should be withdrawn gradually when discontinuing to avoid withdrawal symptoms.[70] Gabapentin (Neurontin) has been shown to significantly reduce hot flashes. Common side effects included somnolence and dizziness. It appears to be more modest in its impact on hot flashes than SSRIs.[71]

Historically, other medications have been used for treating hot flashes (e.g., Bellergal), but these are associated with limited efficacy and/or toxicity.[72–74] Transdermal clonidine (100-μg patch changed weekly) has been used but is only slightly more effective than placebo.[75] With other currently available effective therapies, treatments with limited effectiveness and/or frequent side effects are of mostly historical significance.

Weight loss and regular exercise may be helpful in reducing bothersome hot flashes. Dressing in layers, keeping bedroom temperatures cool, and avoiding alcohol and caffeine are also recommended as lifestyle interventions to reduce hot flashes. Alternative therapies for vasomotor symptoms are also discussed in Chapter 20.

Genitourinary Atrophy

Although vasomotor symptoms often are experienced early in the menopausal transition, the effects of estrogen deficiency on the genitourinary tissues are usually later in onset. Also, while vasomotor symptoms tend to decrease with time after the FMP, frequency and severity of genitourinary atrophy increase as time from the FMP progresses. Estrogen presence makes the vaginal mucosa thicker and surface epithelial cells richer in glycogen. Surface epithelial glycogen helps promote the presence of lactobacilli in the vagina and therefore maintenance of normal vaginal pH. The maintenance of normal vaginal pH is an important defense mechanism against vaginal infection. Lower estrogen levels lead to thinner, paler, and dryer vaginal mucosa, which can lead to a sensation of dryness, irritation, and itching. Lack of estrogen can also affect the collagen in the vaginal walls with consequent loss of elasticity and a decrease in vaginal caliber, especially at the introitus, as well as a decrease in vaginal length. All of these changes may lead to the experience of pain with sexual activity, especially vaginal penetration.

The thinner vaginal mucosa is also more susceptible to traumatic injury from sexual activity or even from friction with washing and wiping after urination or bowel movements. Atrophic vaginitis, presenting with acute onset burning and watery discharge, can occur as well. Exposure to previously innocuous chemicals found in some soaps and detergents can become a source of irritation. Because the epithelium lining the urinary tract are also estrogen dependent, dysuria, urinary frequency and urgency, as well as increased susceptibility to urinary tract infection may also occur as a consequence of lower estrogen levels after menopause.[76,77]

While nearly all women note a change in vaginal secretions after menopause, at least 50% of postmenopausal women experience some form of bothersome genitourinary symptoms.[78] These symptoms can significantly affect a woman's sexual, emotional, mental, and physical quality of life, resulting in social isolation and low self-esteem.[79] Atrophy symptoms are underreported and may often only be elicited with direct questioning about sexual comfort, urinary function, and vaginal sensation. As women's life expectancy increases, increased attention needs to be paid to the physiologic but often bothersome genitourinary changes accompanying the postmenopausal state. While gross atrophic changes in the external genitalia and vaginal mucosa are often obvious on exam, it is still important to rule out other causes such as vaginal infection or chemical irritation when women present with symptoms of vaginal irritation and/dyspareunia. A careful history regarding potential exposure to irritants as well as measurement of vaginal pH and microscopic examination of vaginal secretions is indicated. Examination and wet mount findings seen with atrophic change are summarized in Table 24.2. When examining postmenopausal women, external skin changes from atrophy can be difficult to distinguish from dystrophic, dysplastic, and neoplastic changes. Biopsy is often indicated to rule out more serious pathology, especially if skin changes do not respond to topical estrogen therapy.

Therapeutic Options

Genitourinary atrophy symptoms are clearly related to level and duration of estrogen deficiency. These symptoms are less common in postmenopausal women being treated with systemic estrogen therapy, with or without addition of progesterone. However, the amount of systemic estrogen needed to satisfactorily treat vasomotor symptoms may not be enough to treat atrophy symptoms.[80] Conversely, local treatment of atrophy symptoms with vaginally applied estrogens will usually not cause enough systemic absorption to treat vasomotor symptoms. The effectiveness of vaginal estrogen treatment for atrophy symptoms has been well documented.[81] Current vehicles available in the United States for localized vaginal estrogen treatment include vaginal creams, vaginally inserted tablets, and vaginally inserted long-acting rings

TABLE 24.2 Vaginal Atrophy Findings

Microscopy	Increased basal/parabasal, decreased superficial cells May see increased WBC and RBC from trauma	Larger nuclei; less cytoplasm; smaller, rounder epithelial cells; absence of other pathogens (i.e., yeast, *Trichomonas*, clue cells)
pH of vaginal secretions	>5	
Gross appearance	Mucosa thin, flat, shiny; minimal secretions or thin watery secretions Labial fusion at midline and/or laterally Shrunken labia Introital narrowing Fissures superficial at introitus	

WBC, white blood cell; RBC, red blood cell.

TABLE 24.3 Vaginal Estrogen

Medication	Dosing Interval	Advantage	Disadvantage
Vaginal estradiol tablet 25 mcg or 10 mcg	Initiate daily for 2 weeks then maintain at twice weekly	Less messy than cream, multiple doses available Disposable applicator with each dose	May be difficult to remember twice weekly dosing
Cream—estradiol or conjugated estrogen	Initiate daily for 2 weeks then maintain at twice weekly	Can adjust dose Reusable applicator difficult for some patients to clean Can be used externally for vulvar symptoms	May be difficult to remember twice weekly dosing
Estradiol vaginal ring	Change every 3 months	Only needs attention every 3 months	Reluctance to use retained ring

(see Table 24.3). All are effective and in general well tolerated with few systemic side effects when used at doses intended for treatment of atrophy. Each currently available option has advantages and disadvantages. While creams have the most flexibility in dosing options, women often find them messy to use and may have issues with cleaning and reusing the applicator. Vaginally inserted estradiol containing tablets currently have two dosing options are less messy to use and come with individual applicators for each dose. Usual maintenance dose for both cream and tablets is twice weekly, an interval that may be more difficult to comply with. Estradiol containing rings are inserted vaginally and changed every 3 months. Although this dosing interval is more convenient, many women are not comfortable inserting and/or retaining the ring.

Systemic absorption of vaginally applied estrogens is a concern, especially in regard to elevation of risk of endometrial hyperplasia and cancer with prolonged unopposed estrogen stimulation of the endometrium. To date, studies of the endometrial effects as well as other side effects indicating systemic absorptions (i.e., breast pain and tenderness) of standard doses of vaginal estrogen-containing rings, creams, and tablets have been reassuring for the most part. In isolated studies, vaginal bleeding and breast tenderness and endometrial effects have been associated with use of conjugated equine estrogen (CEE)–based creams but other studies have not confirmed these effects.[82] To date, there is no evidence that standard doses of vaginal estrogen for atrophy increases breast cancer risk or risk of recurrence in breast cancer survivors. However, this area has not been well studied. Studies do show much lower to absent systemic absorption of vaginal estrogens at standard doses and vehicles used for atrophy treatment as compared to systemic oral or transdermal administration.[83] While systemic use of hormonal therapy for the treatment of menopausal symptoms remains controversial, vaginal estrogen use appears to be a safe and effective option for treatment of the very common symptoms caused by postmenopausal genitourinary atrophy.

Sexual Function

Female sexuality and sexual function is a complex blend of physiologic function, individual sexual identity, and other psychological influences. Definition of female sexual dysfunction (FSD) during and after the menopausal transition is not "one size fits all" but rather an individualized diagnosis that needs to encompass physical, psychological, and relationship aspects. Despite the popular belief that sexuality is not a part of an elderly person's life, studies show that between 50 and 80% of older people have an interest in sex or are sexually active.[84] It appears that the degree of continued sexuality activity depends on the physical condition of each partner and the strength of their relationship.[85,86]

Several definite changes affecting sexual function occur with the onset of menopause. Declining estrogen levels result in decreased vaginal lubrication and genital atrophy. Intercourse may be uncomfortable and associated with the sensation of burning, irritation, and spotting. Lubricants, estrogen therapy (vaginal and/or systemic), and regular sexual activity alleviate these symptoms.[87] In addition to improving lubrication and elasticity of the vaginal mucosa, estrogen improves blood flow to the vagina and clitoris and modulates the sensory threshold in the vagina and external genitalia.

While atrophy symptoms can be fairly easily treated (see earlier discussion), understanding the effect of menopause on libido or sexual desire is more complex. Loss of libido is noted to occur and be problematic for many postmenopausal women.[88] There is some evidence that hormone therapy results in improved arousal and sexual desire.[89,90] Data regarding the effect of oral testosterone on sexual activity, satisfaction, and orgasm are mixed.[90,91] Recent meta-analysis looking at the use of testosterone in addition to estrogen therapy concluded that adding testosterone to hormone therapy regimens in postmenopausal women seemed to improve sexual function.[92] However, to date, in the United States, there is no commercially available FDA-approved testosterone for women except when used in combination with oral estrogens (see Treatment section). Large, randomized controlled trials examining the utility of a testosterone matrix patch for women for the treatment of sexual dysfunction during menopause are currently underway. Efficacy of the testosterone patch in combination with hormonal therapy has been shown in improving total satisfying sexual activity when compared to placebo in surgically and naturally menopausal women with the diagnosis of hypoactive sexual desire disorder (HSDD).[93,94] In addition, studies of the testosterone matrix patch in postmenopausal women with HSDD not using hormone therapy showed increased desire and satisfying sexual experiences. Vaginal bleeding

occurred more in treatment than placebo group but no endometrial hyperplasia or cancers were found on subsequent testing.[95] Although short-term study of transdermal testosterone supplementation for the treatment of postmenopausal HSDD is encouraging, long-term safety and effectiveness data for exogenous androgens in women are still needed.

Oral dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEA-S) supplements are available in the United States over the counter in varying doses, but there are no national quality control standards or oversight for these products. The bioavailability of DHEA-S varies by manufacturer. Results on the use of these androgens for menopausal symptoms and sexual dysfunction have been conflicting.[96,97]

Other medications have been studied for effectiveness with postmenopausal HSDD in women. Studies of sildenafil have yielded conflicting results. Dopaminergic drugs, such as bupropion, have been studied as well without conclusive results.[98] It is important to remember that many factors can contribute to HSDD in both pre- and postmenopausal women. Chronic diseases and their medical treatments as well as underlying depression can affect a woman's individual sexual desire and response. Issues in relationships can also influence sexual desire and response. As the population of postmenopausal women grows, we can expect more attention to the options available for postmenopausal women with issues with sexual function and desire.

Skin

With aging, the amount of collagen declines and thinning of the skin occurs; this results in decreased elasticity, wrinkling, and dryness. Because skin contains estrogen receptors, declining estrogen levels are believed to play a role in the skin changes that occur after menopause.

Several studies reveal that either systemic or topical estrogen treatment can protect a woman from these changes.[99–104] One observational study of 3875 postmenopausal women found that ever-users of estrogen were 30% less likely to suffer from dry and wrinkled skin than never-users.[102] There is some evidence that continuous hormone therapy (HT) is associated with greater skin thickness than sequential administration.[103] Avoidance of sun exposure, especially in women with fairer skin tones, improves skin quality. Commercially available moisturizers and exfoliates are also available both over the counter and by prescription. A thorough discussion of treatment options for skin aging is beyond the scope of this chapter.

Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death in women in the United States. In 2006, 1 in 2.8 deaths in American women was from CVD, whereas only 1 in 4.5 deaths was from cancer. More women in the United States die from heart disease than from the other leading causes of death including cancer, chronic lower respiratory diseases, Alzheimer disease, and accidents combined.[104]

After menopause, women's risk for coronary heart disease (CHD) rises. Postmenopausal status is counted with the same importance as male sex in the National Cholesterol Education Program (NCEP) risk factors for CHD. The major risk factors for CHD can be divided into modifiable and nonmodifiable factors (Table 24.4).[105]

The strongest predictor of CHD in women is low high-density lipoprotein (HDL) cholesterol.[106] Diabetes and dyslipidemia have been identified as more powerful risk factors in women compared with men.[107] In fact, women with diabetes lose their premenopausal estrogen advantage and are at equal risk as men of developing coronary artery disease (CAD) in their forties.[108]

Metabolic syndrome characterizes commonly grouped risk factors associated with both CHD and type 2 diabetes. This syndrome results partly from heredity but is strongly influenced by obesity and inactivity. The prevalence of metabolic syndrome in the United States was 32.6% in women older than 20 years of age between 2003 and 2006.[104,109] The American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement[110] defines the diagnosis of metabolic syndrome when three or more of the following five risk factors are present:

1. Fasting blood sugar over 100 or active treatment for elevated blood sugar
2. HDL <50 (for women) or active treatment for elevated lipids
3. Triglycerides >150 or in treatment for elevated triglycerides
4. Waist circumference >88 cm (for women)
5. Blood pressure >130/85 mm Hg or active treatment for hypertension

Women should be screened for hyperlipidemia through a fasting lipid profile, which should include total cholesterol, low-density lipoprotein (LDL), HDL, and triglyceride levels (Table 24.5). In addition, elevation

TABLE 24.4 The Major Risk Factors of Coronary Heart Disease

Modifiable	Nonmodifiable
Elevated LDL Low HDL (less than 50) Elevated triglycerides	Increasing age (older than 55 years of age)
Hypertension	Male sex
Diabetes	Family history of premature CHD (first degree younger than the age of 65 years in women, younger than 55 years of age in men)
Physical inactivity	Postmenopausal status
Obesity	Personal history of CHD
Smoking	

LDL, low-density lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease.

TABLE 24.5 Clinical Guidelines for Cholesterol Testing and Management

Step 1

Determine patient's LDL, total, and HDL cholesterol levels (mg/dL) after a 9- to 12-hour fast:
- LDL cholesterol—primary target of therapy
  - <100 Optimal
  - 100–129 Near or above optimal
  - 130–159 Borderline high
  - 160–189 High
  - ≥190 Very high
- Total cholesterol
  - <200 Desirable
  - 200–239 Borderline high
  - ≥240 High
- HDL cholesterol
  - ≤40 Low
  - ≥60 High

Step 2

Identify any other atherosclerotic diseases that confer high risk for coronary heart disease (CHD) events (CHD risk equivalent):
- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm
- Diabetes

Step 3

Determine presence of major risk factors (other than LDL) that modify LDL goals:
- Cigarette smoking
- Hypertension (BP ≥140/90 mm Hg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)*
- Family history of premature CHD (CHD in male first-degree relative younger than 55 years; CHD in female first-degree relative younger than 65 years)
- Age (men older than or at 45 years of age; women older than or at 55 years of age)

*HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

Step 4

If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk using Framingham tables.
- There are three levels of 10-year risk:
- >20%—CHD risk equivalent
- 10–20%
- <10%

Step 5

Determine risk category:
- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cut Points for Therapeutic Lifestyle Changes (TLCs) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal	LDL Level at Which to Initiate TLCs	LDL Level at Which to Consider Drug Therapy
CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100–129 mg/dL: drug optional)*
2+ Risk factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10–20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0–1 Risk factor**	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by TLCs. Others prefer use of drugs that primarily modify triglycerides and HDL (e.g., nicotinic acid or fibrate). Clinical judgment may also call for deferring drug therapy in this subcategory.
**Almost all people with 0–1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0–1 risk factor is not necessary.

Step 6

Initiate TLC if LDL is above goal:
- TLC diet
  - Saturated fat <7% of calories, cholesterol <200 mg/day
  - Consider increased viscous (soluble) fiber (10–25 g/day) and plant stanols/sterols (2 g/day) as therapeutic options to enhance LDL lowering
  - Weight management
- Increased physical activity

Step 7

Consider adding drug therapy if LDL exceeds levels shown in Step 5 table.
Consider drug simultaneously with TLC for CHD and CHD equivalents
Consider adding drug to TLC after 3 months for other risk categories

(continues)

TABLE 24.5 Clinical Guidelines for Cholesterol Testing and Management *(Continued)*

Step 8

Identify metabolic syndrome and treat, if present, after 3 months of TLC Clinical Identification of the Metabolic Syndrome—Any Three of the Following:

Risk Factor	Defining Level
Abdominal obesity*	Waist circumference**
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.
**Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (e.g., 94–102 cm [37–39 in]). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similar to men with categorical increases in waist circumference.

Treatment of the metabolic syndrome
Treat underlying causes (overweight/obesity and physical inactivity):
Intensify weight management
Increase physical activity
Treat lipid and nonlipid risk factors if they persist despite these lifestyle therapies:
Treat hypertension
Use aspirin for CHD patients to reduce prothrombotic state
Treat elevated triglycerides and/or low HDL (as shown in Step 9)

Step 9

Treat elevated triglycerides
ATP III Classification of Serum Triglycerides (mg/dL)

<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

Treatment of elevated triglycerides (≥150 mg/dl):
Primary aim of therapy is to reach LDL goal
Intensify weight management
Increase physical activity
If triglycerides are ≥200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total – HDL) 30 mg/dL higher than LDL goal

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD risk equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) risk factors and 10-year risk ≤20%	<130	<160
0–1 Risk factor	<160	<190

If triglycerides 200–499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal:
Intensify therapy with LDL-lowering drug, or
Add nicotinic acid or fibrate to further lower VLDL
If triglycerides ≥500 mg/dL, first lower triglycerides to prevent pancreatitis:
Very low-fat diet (≤15% of calories from fat)
Weight management and physical activity
Fibrate or nicotinic acid
When triglycerides <500 mg/dL, turn to LDL-lowering therapy
Treatment of low HDL cholesterol (<40 mg/dL):
First reach LDL goal, then intensify weight management and increase physical activity.
If triglycerides 200–499 mg/dL, achieve non-HDL goal.
If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent, consider nicotinic acid or fibrate.

Adapted from the U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute ATP III At-A-Glance: Quick Desk Reference. NIH Publication No. 01-3305. May 2001. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm. Accessed June 28, 2005.
Based on the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel or ATP III).

TABLE 24.5 Clinical Guidelines for Cholesterol Testing and Management *(Continued)*

Framingham Risk Estimate Charts

Estimate of 10-Year Risk for Men (Framingham Point Scores)		Estimate of 10-Year Risk for Women (Framingham Point Scores)	
Age	**Points**	**Age**	**Points**
20–34	–9	20–34	–7
35–39	–4	35–39	–3
40–44	0	40–44	0
45–49	3	45–49	3
50–54	6	50–54	6
55–59	8	55–59	8
60–64	10	60–64	10
65–69	11	65–69	12
70–74	12	70–74	14
75–79	13	75–79	16

	Points				
Total Cholesterol	**Age 20–39**	**Age 40–49**	**Age 50–59**	**Age 60–69**	**Age 70–79**
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
Total Cholesterol	**Age 20–39**	**Age 40–49**	**Age 50–59**	**Age 60–69**	**Age 70–79**
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20–39	**Age 40–49**	**Age 50–59**	**Age 60–69**	**Age 70–79**
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

	Points				
	Age 20–39	**Age 40–49**	**Age 50–59**	**Age 60–69**	**Age 70–79**
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	−1
50–59	0
40–49	1
40	2

HDL (mg/dL)	Points
≥60	−1
50–59	0
40–49	1
<40	2

(continues)

TABLE 24.5 Clinical Guidelines for Cholesterol Testing and Management *(Continued)*

Framingham Risk Estimate Charts

Estimate of 10-Year Risk for Men			Estimate of 10-Year Risk for Women		
Systolic BP (mm Hg)	**If Untreated**	**If Treated**	**Systolic (mm Hg)**	**If Untreated**	**If Treated**
<120	0	0	<120	C0	0
120–129	0	1	120–129	1	3
130–139	1	2	130–139	2	4
140–159	1	2	140–159	3	5
≥160	2	3	≥160	4	6

Point Total	10-Year Risk %	
<0	<1	
0	1	
1	1	
2	1	
3	1	
4	1	
5	2	
6	2	
7	3	
8	4	
9	5	
10	6	
11	8	
12	10	
13	12	
14	16	
15	20	
16	25	
≥17	≥30	10-Year risk__%

Point Total	10-Year Risk %	
<9	<1	
9	1	
10	1	
11	1	
12	1	
13	2	
14	2	
15	3	
16	4	
17	5	
18	6	
19	8	
20	11	
21	14	
22	17	
23	22	
24	27	
≥25	≥30	10-Year risk__%

Adapted from National Cholesterol Education Program. Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. NIG Pub. No 02-5215. Bethesda, MD: National Heart, Lung, and Blood Institute, 2002, with permission.

of serum C-reactive protein was found to be a strong independent risk factor for CHD in the Women's Health Initiative (WHI).[111]

Although the goal of therapy for dyslipidemia depends in part on risk factors, the primary goal is reduction of LDL cholesterol. Statins are the first-line therapy for lowering LDL, and clinical trials have demonstrated a marked reduction in clinical cardiovascular events in women using cholesterol-lowering drugs.[112] For women, measurement of non–HDL-cholesterol (HDL-C) by subtracting HDL from total cholesterol may give a better measurement of the amount of LDL lipoprotein particles than LDL-cholesterol measurement. This is because non–HDL-C measurement takes triglyceride levels and insulin resistance important in women's risk valuation into the calculation. Treatment with statins should be considered for at-risk women with non–HDL-C >120 and for very high-risk women with non–HDL-C >80.[113] Recent data also suggests that statin treatment in men and women with LDL <130 and elevated C-reactive protein over 2.0 mg/L reduced CVD endpoints of myocardial infarction, stroke, and death from CVD.[114] Control of any elevation of blood sugar and treatment of underlying hypertension are also important in CHD risk reduction strategies. In addition, recommending modification of modifiable risk factors by encouraging weight loss and physical activity as well as smoking cessation is applicable to all women.

Prior to the publication of the results of the combination treatment arm of the WHI study in 2002, most observational studies seemed to indicate that

postmenopausal HT reduced CHD risk. Initial WHI data, however, showed an elevation of risk of nonfatal myocardial infarction (MI) in postmenopausal women treated with combination HT.[5] More recent analysis of the WHI data has suggested that elevation in risk for women taking HT may be limited to women initiating HT remote from menopause. In addition, other randomized studies of HT suggest no increase (and possible reduction) in CHD risk when initiated less than 10 years after menopause.[115]

Stroke and Venous Thromboembolic Events

Stroke is the third leading cause of death in the United States and affects one in five women. Although the incidence for stroke is about the same for men and women, at all ages, more women will die of stroke than men. Stroke rate doubles each decade after age 55 years. The most common type of stroke is atherothrombotic, accounting for 61% of all strokes. These strokes usually occur at atherosclerotic sites and lead to ischemic injury. The second most common type of stroke is cerebral embolus, accounting for 5 to 14% of all strokes.[116] Risk factors for stroke include age, race, gender, and family history. A positive family history of stroke or transient ischemic attack almost doubles the risk of stroke. African Americans have the highest rates of stroke. Many studies have looked at the relationship between menopause and postmenopausal HT and stroke with varying results. Different studies comparing postmenopausal women taking HT have shown no effect, increased, and decreased risk of stroke. Those showing increased risk of stroke with the use of HT (including the WHI) have demonstrated an increase in thrombotic but not hemorrhagic stroke. As with other cardiovascular-related risk elevation in the WHI data, risk elevation seems to be clearer in older women who started HT remote from menopause. In addition, transdermal estrogen therapy may have less of an effect on stroke risk than oral HT (see Treatment section).[117]

In general, lifestyle interventions that decrease CVD risk in general such as exercise, weight loss, smoking cessation, and optimum management of diabetes and hypertension are strategies to decrease risk of stroke as well. Low-dose aspirin treatment is effective in decreasing stroke risk in all women older than 65 years of age and is also recommended for higher risk women younger than 65 years of age.

Venous thromboembolism (VTE) is the general term that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE has a yearly first-time incidence in the United States of about 100 cases per 100,000 persons. The incidence varies by, and increases with, age; there are approximately 500 cases per 100,000 (0.5%) in people 80 years of age and older. Of patients with VTE, close to two-thirds have DVT alone and about one-third concomitant with PE.[76] VTE has a high recurrence rate, especially in the first few months after the initial event; the recurrence rate at 6 months is approximately 7%.[118] The classic triad of risk factors for VTE is hypercoagulability, stasis, and endothelial injury. However, in 25 to 50% of patients with first-time VTE, no identifiable risk factors exist.[118]

Risk factors for VTE may be general, acquired, or inherited. Known heritable mechanisms include antithrombin deficiency and protein C and protein S deficiencies. Although it is important to identify these conditions because of the heightened risk of VTE, their overall contribution to the incidence of recurrent VTE is less than 10%.[119] Most activated protein C resistance is due to a mutation in the factor V gene, also known as factor V Leiden. Elevated levels of specific coagulation factors are associated with increased risk of VTE, particularly factor VIII. The exact relationship between hyperhomocysteinemia and VTE risk is not currently known.[118] While menopausal status has not been shown to be a factor in elevation of VTE risk, VTE risk was elevated in the HT treatment arm of the WHI study, especially in the first year of treatment.[5] Prevention of VTE is centered on avoidance of high-risk circumstances such as prolonged immobility and prophylaxis of appropriate people with anticoagulation after a VTE event and surrounding high-risk surgical procedures. Further discussion of the prevention of VTE is beyond the scope of this chapter.

Osteopenia/Osteoporosis

Osteoporosis and its associated increase in fracture risk is a common problem for women as they age (Table 24.6). For example, it is estimated that a white American woman at age 50 years has a 40% risk of suffering an osteoporosis-related fracture in her lifetime.[120] The hip, vertebrae, and wrist are the most common fracture sites in osteoporotic women. It is estimated that two-thirds of osteoporosis fractures occur after age 75 years.[121] Hip fractures are associated with a 25% increase in mortality in the year after the fracture. In addition, after hip fracture, 50% of women suffer some long-term loss of mobility. Hip fracture is commonly the event that causes a woman to lose her independence; 25% of women require long-term care after hip fracture. Only 40% of hip fracture patients regain their previous level of mobility, and one-third will break the opposite hip in the future.[122] Vertebral fractures can also cause pain, loss of height, and kyphosis. Thoracic vertebral fractures can cause restriction on respiratory and digestive functions.[123]

Bone mass is a major factor influencing risk for fracture. Throughout a woman's life, bone is constantly resorbing and reforming. Bone mass is determined by the balance between these processes. Formation initially exceeds resorption and this causes peak bone mass to be achieved between 20 and 30 years of age.[124]

TABLE 24.6 Risk Factors for Osteoporosis

Nonmodifiable	Female gender First-degree relative with osteoporosis Caucasian or Asian Body mass index less than 20 Age	Diseases	AIDS/HIV Chronic liver or renal disease Inflammatory bowel disease Depression Insulin-dependent diabetes Chronic obstructive pulmonary disease Cushing disease Multiple myeloma Multiple sclerosis Rheumatoid arthritis Thyrotoxicosis Hyperparathyroidism Lymphoma, leukemia Eating disorders Pernicious anemia Estrogen deficiency at early age (younger than 45 years of age)
Modifiable	Low calcium intake Vitamin D deficiency Amenorrhea Excessive alcohol use Smoking Sedentary lifestyle		
Drugs	Premenopausal tamoxifen Thyroxine Warfarin or heparin GnRH agonists Immunosuppressives Anticonvulsants Lithium Medroxyprogesterone acetate Cytotoxic agents Excessive use of aluminum-based antacids		

GnRH, gonadotropin-releasing hormone.

After approximately 30 years of age, resorption begins to exceed formation and bone mass declines gradually at a rate of approximately 0.4% per year until the menopause. With menopause, there is an increase in resorption over reformation causing acceleration in bone loss for the first 5 to 10 years after the FMP. This acceleration of bone loss at the time of menopause seems to be related to loss of estrogen-mediated inhibition of bone resorption.[125] After this period of accelerated loss, age-related bone loss continues at a slower rate. As women age, this loss in bone mass can lead to increased fracture risk with fractures related to bone loss most commonly occurring in the hip, vertebrae, and wrist.[126] Because bone loss accelerates with the menopause, osteoporosis diagnosis and treatment are of particular interest to the gynecologist caring for peri- and postmenopausal women.

Bone mass is higher in African American women and obese women; it is lower in Caucasian, Asian, thin, and sedentary women. Studies indicate that up to 70% of the variation in bone density is secondary to heredity.[127] In addition to age, menopausal status, and genetics, lifestyle factors such as smoking, lower body mass index, and a dietary content low in calcium and vitamin D are associated with lower bone mass. In addition, several medical conditions and medications are associated with lower bone mass (see Table 24.7).[128]

While low bone mineral density (BMD) is one predictor of fracture risk, other clinical risk factors can aid in decision making regarding when to start BMD testing and can also be used as additional factors to take into account along with BMD when making individual treatment decisions.

Diagnosis and Assessment

Evaluation for postmenopausal osteoporosis includes a comprehensive history and physical examination and assessment of risk factors for fractures. Because only approximately one-third of vertebral fractures cause pain, loss of height may be the first sign of vertebral fractures and osteoporosis. Therefore, patients' heights should be recorded at each visit, and any changes in posture noted. It is important to consistently measure heights without shoes because a woman's footwear can cause significant variations in height measurement. In addition, caloric, calcium, and vitamin D intake need to

TABLE 24.7 Medical Conditions and Medications Associated With Lower Bone Mass

Medications	Medical Problems
Overtreatment of hypothyroidism GnRH agonist or analogue treatment (prolonged) Heparin Glucocorticoid use (long term) Aromatase inhibitors Cytotoxic agents Immunosuppressive agents Intramuscular medroxyprogesterone acetate (reversible)	History of anorexia/bulimia Hypercalciuria Hyperthyroidism Hyperparathyroidism Cushing syndrome Vitamin D deficiency Malabsorption syndrome (e.g., celiac disease, Crohn) Chronic liver disease Osteogenesis imperfecta Hypophosphatemia Thalassemia Ankylosing spondylitis Chronic renal disease Multiple myeloma, lymphoma, and leukemia Rheumatoid arthritis

TABLE 24.8 Bone Mineral Density Screening Indications

- All women older than age 65 years
- Postmenopausal women with history of use of long-term medication associated with osteoporosis risk
- Postmenopausal women with medical conditions associated with increased risk of osteoporosis
- Postmenopausal women with history of a fragility fracture
- Postmenopausal women older than age 50 years with a BMI <21 kg/m^2
- History of a parent with a hip fracture
- Current smoker
- Rheumatoid arthritis
- Alcohol intake of more than 2 units per day (1 unit + 12 oz beer, 4 oz wine, 1 oz liquor)

be assessed and advice about how to obtain adequate calcium and vitamin D intake given. Dietary sources of calcium should be encouraged and overuse of supplements discouraged because there is no benefit to consumption of over 1500 mg of calcium per day.

BMD screening should be considered in postmenopausal women younger than 65 years of age with risk factors for osteoporosis and in all women older than 65 years of age, regardless of risk factors[128] (Table 24.8).

Dual energy x-ray absorptiometry (DXA) is currently the gold standard for assessing BMD, specifically at the lumbar spine and femoral neck. Disadvantages of DXA are that it may yield a falsely elevated BMD reading due to poor positioning, disk disease, compression fractures, scoliosis, or vascular calcifications. Because osteoporosis is a silent disease prior to fracture, measurement of bone strength is an important component in the timely diagnosis, treatment, and hopeful prevention of fracture. BMD testing is the most common tool used to measure bone strength. BMD is quantified in grams of mineral/area or volume and is generally measured at the hip and lumbar spine. Other components of bone strength including heterogeneity of bone microstructure, collagen structure, and hydroxyapatite do not yet have a practical clinical measure.

Results from BMD testing are standardized for reporting purposes into T and Z scores. T scores compare measured BMD to the mean BMD of normal gender matched 30 year olds and are useful for evaluation of fracture risk in postmenopausal women. Z scores compare measured BMD to a reference population of the same gender, age, and ethnicity. Z scores are used in evaluating BMD in premenopausal women. According to the World Health Organization (WHO) and the International Society for Clinical Densitometry, for postmenopausal women, osteoporosis is defined as a T score less than 2.5 in the total hip, femoral neck, or lumbar spine (in at least two vertebral areas measured in the anterior–posterior projection). Osteopenia or low bone mass is defined as T scores between −1 and −2.5, T scores above −1 are considered normal.[129] When measurement of spine or hip because of anatomic (e.g., scoliosis) or prior surgery (e.g., hip replacement) is not feasible, the distal third of the radius can be measured as well. However, there is currently less data regarding radius BMD and fracture risk.

When a patient suffers a fragility fracture, the diagnosis of osteoporosis can also be made clinically, regardless of BMD.

Bone turnover may be measured through a variety of serum or urinary markers. The markers may be classified as (a) enzymes or proteins that are secreted by osteoblasts or osteoclasts or (b) substances produced during the formation or breakdown of type I collagen, the principal protein of the bone matrix. Bone markers are often categorized as being either bone formation or bone resorption markers. Marker measurements correlate poorly with BMD and osteoporosis diagnosis. The precise clinical role for bone biomarkers in the management of osteoporosis has not been established because their ability to predict fracture risk in treated patients has not been reproducible or consistent.[128] If osteoporosis is diagnosed, laboratory evaluation for secondary causes should be ordered; these tests may include complete blood count (CBC), serum calcium, alkaline phosphatase, phosphate, creatinine, albumin, 25-OH vitamin D, and thyroid-stimulating hormone, as well as 24-hour urinary calcium excretion. When BMD scores are less than expected in relationship to an individual's risk factors or when patient symptoms indicate, tests for less common causes of secondary osteoporosis such as 24-hour free urinary cortisol (Cushing disease), serum protein electrophoresis (multiple myeloma), serum parathyroid hormone (PTH) level (hyperparathyroidism), and tissue transglutaminase antibody (celiac disease) should be considered. More than one-third of women with osteoporosis have at least one coexisting condition that contributes to low BMD, and this must be taken into account when assessing a woman's risk for fracture.

Treatment

It has been shown that a substantial proportion of women will initiate treatment and change behaviors after they have been diagnosed with either osteopenia or osteoporosis.[130] All postmenopausal women should be encouraged to obtain adequate calcium and vitamin D, avoid smoking and excessive alcohol intake, and participate in weight-bearing exercise. Discussion of fall prevention measures is also important, especially in women known to be at increased risk of fracture.

The diets of women from the United States are generally deficient in calcium. Adequate calcium intake is critical to establishment of peak bone mass and prevention of subsequent bone loss. Although there is not a reliable lab test for deficient calcium intake, a 24-hour urinary calcium of less than 50 mg would indicate either poor intake or absorption of calcium. Multiple organizations support the current recommendations for calcium intake of 1200 to 1500 mg/day of elemental calcium

for women older than 50 years of age. Dietary sources of calcium should be recommended. In addition, calcium-fortified foods and supplements are commonly available. In calculating supplement dosage, elemental calcium should total 1200 to 1500 mg/day. Calcium is better absorbed when dosage is no more than 600 mg at one time. Constipation is the most common side effect of calcium supplementation. There are many calcium supplement available including chewable and liquid varieties. Calcium supplements should be avoided in women with calcium containing renal calculi. There does not appear to be a benefit to consumption of over 1500 mg/day.[128]

Vitamin D deficiency is also very common in postmenopausal women and in the older population in general. Vitamin D is critical for intestinal absorption of calcium. Vitamin D can be produced from precursors when the skin is exposed to ultraviolet rays from the sun. Avoidance of sun exposure and lack of vitamin D–rich foods in the American diet contribute to deficiency. Postmenopausal women should be encouraged to consume 1000 IU of vitamin D per day. This can be obtained from supplements, fortified food products (e.g., milk and many cereals), and fatty fish. Serum 25(OH) D levels can be measured and temporary additional supplementation can be recommended when levels are low. However, prolonged exposure to higher doses should be avoided because hypercalciuria and hypercalcemia have been associated with vitamin D doses above 10,000 IU/day.[128] There is emerging evidence that vitamin D intake of over 700 to 800 IU/day is associated with decreased fracture risk. Vitamin K and magnesium and isoflavones are often promoted as other supplements that are helpful in reducing fracture risk. Data supporting their effectiveness for fracture prevention in is currently lacking.

In addition to adequate calcium and vitamin D consumption, weight-bearing exercise is known to be important for development and maintenance of bone strength. To benefit bones, weight-bearing exercise does not need to be intense. In addition to active weight-bearing and strength training exercises, whole body vibrations systems also show some promise as a tool to strengthen bones.[131] Women with osteoporosis should be cautioned to avoid exercises where they are likely to fall such as skiing, ice skating, and high-impact and step aerobics.

Because nearly 90% of all nonvertebral fractures are caused by falls,[132] interventions and counseling aimed at fall prevention are important for all postmenopausal women. Muscle strength training and balance exercises for all women help to reduce the risk of falls and subsequent injury and are possible to some extent even in the most physically impaired and fragile women. Attention to medication interactions and avoidance of overuse of sedating/psychotropic drugs is also important. Review of footwear and potential fall hazards in the home may be helpful in at-risk women.

Although dietary and lifestyle interventions and advice are applicable to all peri- and postmenopausal women, pharmacologic agents are also indicated for the treatment in women at high risk of experiencing a fracture related to bone loss. In general, postmenopausal women who have already experienced an osteoporosis-related hip or vertebral fracture are candidates for treatment as are postmenopausal women with BMD diagnosis of osteoporosis. In addition, pharmacologic treatment should be offered to women with a 10-year risk greater than 3% for hip fracture and 20% for other major osteoporotic fracture as calculated by the FRAX tool. The FRAX tool, endorsed by the WHO, incorporates other fracture risk factors including age, sex, weight and height, prior fracture history, parent hip fracture history, alcohol and tobacco use, other causes of secondary osteoporosis, long-term glucocorticoid use, and rheumatoid arthritis along with femoral neck BMD into a statistical model. This model calculates 10-year risk for hip and other major osteoporotic fractures. It is available at http://www.shef.ac.uk/FRAX.[133]

Agents currently available in the United States for the treatment of osteoporosis include both oral and intravenous bisphosphonates, selective estrogen receptor modulators (SERMs), estrogen, PTH, and calcitonin. To date, there are no studies comparing the effectiveness in preventing fractures among these agents.

Bisphosphonates inhibit osteoclast activity and therefore are antiresorptive agents. They are generally felt to be the first-line drug treatment for postmenopausal osteoporosis. All have been shown to reduce fracture risk in postmenopausal women with osteoporosis. Patients with low serum calcium should not take bisphosphonates. Oral forms of the medication need to be taken on an empty stomach and the patient must remain upright and avoid oral intake of anything except water for at least 30 and up to 60 minutes after taking the medication. Daily (alendronate, risedronate, and ibandronate), weekly (alendronate and risedronate), and monthly (risedronate and ibandronate) dosing is available. Intravenous bisphosphonates are available with annual (zoledronic acid) and every 3 months (ibandronate) dosing.

Esophageal and gastric irritation is the most common short-term side effect of the oral bisphosphonates. Intravenous forms of the bisphosphonates have not been associated with gastrointestinal side effects. However, transient flulike symptoms have been reported in association with higher dose bisphosphonates and occur more commonly with annual or every 3 months IV dosing than monthly oral use. These symptoms are self-limited and decrease with subsequent dosing.[128]

Recent case reports have raised concerns regarding unusual and poorly healing fractures of the femur in patients taking long-term bisphosphonates. It is not yet clear whether this is related to theoretical concern about oversuppression of bone turnover as the cause of these fractures and subsequent poor healing or

whether these fractures are a result of underlying severe osteoporosis.[134,134a] Further study is certainly forthcoming in this area.

Also, observations have been made of delayed healing in the jaw (osteonecrosis of the jaw) after dental extraction in patients taking IV bisphosphonates for the treatment of cancer-related bone disease. There have also been case reports of similar issues in patients being treated for osteoporosis with oral bisphosphonates.[135] The incidence of this complication in people being treated for osteoporosis with bisphosphonates, as well as clear causation of this complication by these medications has yet to be elucidated and also warrants further study. Although there is not yet sufficient data to determine optimum length of treatment for postmenopausal women with osteoporosis, it appears that after 5 years of treatment with alendronate, bone density remains stable for up to 5 years after discontinuation of treatment.[136] There is conflicting data so far on fracture risk when comparing continuation to discontinuation of therapy after 5 years of use.[128] More definitive information should be available to guide treatment decisions as our understanding of the long-term risks and benefits of bisphosphonates evolves.

The SERM raloxifene has FDA approval in the United States for the treatment and prevention of postmenopausal osteoporosis. In addition to osteoporotic fracture reduction and improvement in BMD,[137] raloxifene has been shown to decrease the risk of invasive breast cancer by 60 to 70%.[138] However, raloxifene use is also associated with an increased risk of VTE as well as potential exacerbation of vasomotor symptoms.[137,139] Teriparatide, recombinant human PTH, is another FDA-approved postmenopausal osteoporosis treatment; PTH stimulates osteoblast activity and therefore promotes bone formation. Its use to date is reserved for postmenopausal women with osteoporosis and high fracture risk. Teriparatide is administered by daily subcutaneous injection and has been shown to reduce fractures and increases BMD in postmenopausal women with prior vertebral fracture.[140] Side effects include dizziness, nausea, and hypercalcemia. Bone tumors were seen in rat models when higher doses than used in humans were tested. Currently, teriparatide is not indicated for usage for more than 24 months in the United States. Although bone loss resumes after cessation of treatment, using antiresorptive agents after discontinuing teriparatide has been shown to meliorate this bone loss.[141]

Preservation of bone density has long been appreciated as a benefit of systemic estrogen therapy.[142] Importantly, studies have shown a reduction of fracture risk in women taking systemic estrogen.[143] Once estrogen therapy is discontinued, bone loss resumes and fracture risk rises. See the following segment on Hormone Therapy for further discussion of systemic estrogen therapy.

When treating postmenopausal osteoporosis, reevaluation of treatment choice, side effects, and BMD should be done periodically. BMD testing interval during treatment should be done at a 1- to 2-year interval, but fracture risk reduction may not be totally reflected in BMD measurement.[128] When monitoring postmenopausal women for bone loss, BMD measurements can be done at a 2- to 5-year interval. Osteoporosis is a common condition in postmenopausal women. Evaluation of long-term effectiveness and side effects of currently available treatments as well as emergence of new treatments will continue to evolve.

Cognitive Changes/Dementia

Alzheimer disease (AD) is the most common cause of dementia. Elderly women have a higher risk of developing AD than elderly men, and although this may be because their life expectancy is longer, the age-specific incidence of AD is higher in women than in men.[144,145] The diagnosis of AD is most often based on the criteria developed by the National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association. Using these criteria, the diagnosis is classified as definite (clinical diagnosis with histologic confirmation), probable (typical clinical syndrome without histologic confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histologic confirmation).[146] Laboratory studies are necessary to identify causes of dementia and coexisting conditions common in the elderly (e.g., thyroid function tests and measurement of the serum vitamin B_{12} level are ordered to screen for alternative causes of dementia). In addition, a CBC, as well as blood urea nitrogen, serum electrolyte, blood glucose levels, and liver function tests should be performed. Depending on the patient's history and exam, other tests may also be indicated. Patients with dementia should have structural imaging of the brain with computed tomography or magnetic resonance imaging at least once as part of the evaluation or care.[147] It is currently believed that the accumulation of beta-amyloid peptide, or A(beta) peptide, is central to the pathogenesis of AD.[148] Alternative hypotheses emphasize the importance of tau proteins, heavy metals, viral infections, or vascular factors.

Several retrospective, observational studies have suggested that cognitive decline and AD occurs less frequently in women with a history of postmenopausal hormonal therapy.[149–151] However, the Women's Health Initiative Memory Study (WHIMS) arm of the WHI did not demonstrate a benefit in dementia prevention in women initiating HT older than 65 years of age. In fact, dementia was diagnosed more frequently among HT users in this study.[152] The difference between observational and study data has been explained with the theory that during the observational study time, women taking HT were generally healthier than women not taking HT and that better underlying general health, not HT, explained the improvement in cognitive outcomes

in women reporting a history of HT ("Healthy Woman Theory"). More recent study has questioned the validity of this explanation.[153] It is possible that timing of exposure to HT may be critical in explaining differing results. WHIMS studied the effects of exposure to HT starting at age 65 years, whereas other studies reflect HT use in the general population where HT is generally initiated at the time of the menopausal transition.[154] Future studies such as the Kronos Early Estrogen Prevention Study (KEEPS) will hopefully help to clarify the role of HT in either preventing or increasing risk for dementia, cognitive decline, and AD. Treatment of AD is best provided by a health care provider with training and experience with this disease and is beyond the scope of this text.

DEPRESSION

Longitudinal studies of women passing through the menopausal transition mostly show an increase in depression during the menopausal transition. This increase in risk for depression wanes in the postmenopausal years.[155-157] Additional studies have shown that a history of premenstrual syndrome or prior depression also contribute to elevation in risk for depression during the menopausal transition.[156,158] In addition to direct effects of loss of estrogen on mood, bothersome vasomotor symptoms, especially with accompanying sleep disturbance, contribute to mood issues during the perimenopausal transition. Study of Women's Health Across the Nation (SWAN) data have consistently shown an increase in irritability and nervousness accompanying the transition.[155,159] In addition, several common life stressors such as children leaving home, caring for aging parents, and the personal onset of physical limitations may accompany the transition through menopause and contribute to mood issues during this time.

JOINT PAIN

Although less well studied than other symptoms accompanying the menopause transition, there is a subset of women who experience abrupt onset of diffuse joint pain during the menopausal transition.[160] In the WHI, joint pain was more likely to be relieved in women in the combination HT group than in the placebo group.[161] Joint pain and arthritis also increase as a normal part of the aging process.

WEIGHT GAIN/DISTRIBUTION

In general, weight trends upward with aging. Basal metabolic rate lowers with age and physical activity generally decreases with aging, contributing to less energy consumption. This coupled with the same or higher caloric intake results in weight gain. Although there is no clear acceleration in weight gain associated with the menopausal transition, after menopause, central weight gain occurs with a change from "pear" to "apple" body shape. This elevation of waist/hip ratio and waist circumference may contribute to elevation in cardiac risk. Postmenopausal HT does preserve a lower waist hip ratio. Several studies have demonstrated that hormone therapy, whether with or without progestins, does not cause an increase in body weight.[162,163]

HORMONE THERAPY

Because natural menopause and aging occur simultaneously, it can be sometimes difficult to distinguish what symptoms are associated with menopause or the menopausal transition, what are the consequences of aging alone and what symptoms may be caused by an independent disease process. Several chronic diseases, such as osteoporosis and CAD, accelerate after menopause. Although it may seem intuitive that replacing ovarian hormones would "treat" those symptoms and disease progression associated with menopause, investigation with prospective randomized trials has not always supported this hypothesis. There is excellent evidence from many studies that estrogen treatment relieves vasomotor and vaginal atrophy symptoms and aids in preservation of bone mass. Although observational studies seemed to indicate that estrogen replacement reduced a woman's chance of developing CAD and AD, more recent prospective, randomized studies have not yielded similar results.

The landmark WHI Study was designed to answer the question of whether a healthy postmenopausal woman would have better health outcomes with or without HT. While continued analysis of the data evolves, WHI data from the combination arm (Table 24.9) showed a significant elevation in stroke, venous thromboembolic events, breast cancer, and nonfatal MI rates in treated versus untreated postmenopausal women. Fractures and colon cancer rates were decreased in treated over untreated women. In a subset of women older than

TABLE 24.9 Women's Health Initiative Combination Arm Outcomes

Rates/10,000 Women/Year	Placebo	CEE 0.625/MPA 2.5 mg	Relative Risk 95% Confidence Interval
Breast cancer	30	38	1.26 (1.00–1.59)
Heart attacks	30	37	1.29 (1.02–1.63)
Stroke	21	29	1.41 (1.07–1.85)
VTE	16	34	2.11 (1.58–2.82)
Colon cancer	16	10	0.63 (0.43–0.92)
Hip fractures	15	10	0.66 (0.44–0.98)

CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; VTE, venous thromboembolism.
From Manson JE, Hsia J, Honson KC, et al.; Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med.* 2003;349:523–534.

TABLE 24.10 Women's Health Initiative Estrogen-Only Arm

Events/10,000 Women/Year	Placebo	CEE 0.625	Relative Risk
Breast cancer	33	26	0.79
Heart attack	54	49	0.91
Stroke[a]	32	44	1.38[a]
VTE	21	28	1.33
Colon cancer	16	17	1.06
Hip fracture[a]	17	11	0.64[a]

CEE, conjugated equine estrogen; VTE, venous thromboembolism.
[a]Significant value.
From The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative Randomized Controlled Trail. *JAMA*. 2004;291:1701–1712.

65 years of age at entry to the study, more women in the combination treatment group developed dementia than in the untreated group.

In the estrogen-only arm of the same study (recruiting only women who had a prior hysterectomy), risk of stroke was increased and risk of fracture was decreased while all other studied outcomes were not significantly different between the groups (Table 24.10).

Subsequent subanalysis of the WHI data has questioned whether elevation of cardiac risk in the combination arm of the study only applies to women initiating HT remote from menopause as opposed to women initiating treatment closer to their FMP.

As our understanding of the risks and benefits of HT continues to develop, HT remains a viable option for many women for treatment of menopausal symptoms after careful consideration of the severity of their symptoms, their personal medical and family histories, and their views of risks and benefits of treatment. When guiding women in this endeavor, there are many options for treatment. Consideration of symptoms needing treatment, presence of an intact uterus, individual patient risk factors, and patient preference for route of administration are all important factors to consider. Terminology surrounding the different permutations and combinations of estrogens and progestins used in treating postmenopausal women is varied and potentially confusing both to clinicians and patients. For the purposes of this chapter, the following terminology will be used:

- HT—hormone therapy, both combined and estrogen alone
- EPT—combined estrogen and progestin treatment
- ET—estrogen therapy

TREATMENT BY SITE OF SYMPTOMS

When the symptoms requiring treatment are limited to those associated with urogenital atrophy, there are a variety of non–hormonally based vaginal lubricants available that may provide satisfactory relief of vaginal dryness and subsequent changes in sexual function. If non–hormonally based vaginal treatments do not provide satisfactory relief, topical and intravaginal treatments designed to treat atrophy with minimal long-term systemic absorption are appropriate (see Table 24.3). No endometrial changes were noted after 1 year of therapy with estradiol containing ring.[164] With the 25-mcg estradiol vaginal tablet placed intravaginally daily for 2 weeks and then twice weekly thereafter, a 6-month study found no change in endometrial thickness.[165] Because distant target site responses have been noted with the use of vaginal estrogens (i.e., change in lipids or bone density), there are some authors that advocate endometrial surveillance after 6 to 12 months of vaginal estrogen use.[166–168]

When the decision has been made to initiate HT for the treatment of vasomotor symptoms, systemic treatment is necessary. Once the decision has been made to treat systemically, the first factor to consider in the decision-making process is whether or not the patient has a uterus. If so, studies clearly indicate that there is an elevation of endometrial cancer risk in women taking systemically absorbed estrogen alone. The addition of appropriate doses of progestational agents eliminates this elevation in risk. Progestational agents can be dosed either in a cyclic or continuous manner. In general, cyclic administration is associated with withdrawal bleeding, whereas the goal of continuous administration is the elimination of bleeding. Bleeding is common with initiation of continuous treatment but generally resolves after 3 to 6 months of treatment in menopausal women. In continuous combined regimens, at 6 months and 12 months, 40 and 60% of patients, respectively, will be amenorrheic.[169,170] Therefore, expectant management for 6 months may be a reasonable approach. Endometrial evaluation is recommended thereafter to exclude endometrial cancer.[171] When HT is initiated prior to completion of the menopausal transition, unpredictable bleeding is a common result. Lower dose combination oral contraceptive pills are generally a better choice if symptom control is needed prior to the FMP.

While both estrogen and progestational agents have data to support their effective relief of vasomotor symptoms, it is the estrogen component of HT that provides superior relief in most women. Therefore, in women who have had a hysterectomy who elect HT for symptomatic relief, estrogen is generally used alone.

Many women are intolerant of the addition of a progestational agent to HT. However, there are multiple progestational agents available. For an individual woman, one agent may be better tolerated than others. There are several oral and transdermal combination estrogen/progestational agent options that are FDA approved for the treatment of vasomotor symptoms, atrophy and prevention of osteoporosis in women with an intact uterus in the United States (Table 24.11). In addition, oral progestational agents can be added at appropriate doses to separately dosed transdermal or oral estrogens.

TABLE 24.11 Available Hormone Therapy Preparations

Brand	Components and Strengths	Route	Recommended Starting Dose
Oral estrogens			
Cenestin	Synthetic CE: 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg	Tablet	0.625 mg daily
Enjuvia	Synthetic CE: 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg		
Estrace	E: 0.5 mg, 1 mg, 2 mg	Tablet	0.5 mg daily
Femtrace	E: 0.45 mg, 0.9 mg, 1.8 mg		
Menest	Esterified estrogens: 0.3 mg, 0.625 mg, 1.25 mg, 2.5 mg	Tablet	0.625 mg daily
Ogen	Estropipate: 0.625 mg, 1.25 mg, 2.5 mg	Tablet	0.625 mg daily
Ortho-est	Estropipate: 0.75 mg, 1.5 mg	Tablet	0.75 mg daily
Premarin	CEE: 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, 2.5 mg	Tablet	0.625 mg daily
Transdermal estrogens			
Alora	E: 0.05 mg/day, 0.075 mg/day, 0.1 mg/day	Patch	0.05 mg/day patch twice weekly
Climara	E: 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1 mg/day	Patch	0.025 mg/day patch once weekly
Divigel	E: 0.25 mg, 0.5 mg, 1 mg/packet	Topical gel	0.5 mg once daily
Elestrin	E: 0.87 g/pump	Topical gel	1 pump daily
Esclim	E: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1 mg/day	Patch	0.025 mg/day patch twice weekly
Estraderm	E: 0.05 mg/day, 0.1 mg/day	Patch	0.05 mg/day patch twice weekly
Estrasorb	E: 1.74 g/pouch	Topical emulsion	2 pouches a day
Estrogel	E:1.25 g/pump	Topical gel	1 pump/day
Evamist	E: 1.53 mg/spray	Topical spray	1–3 sprays/day as needed
Menostar	E: 0.014 mg/day	Patch	Change weekly
Vivelle	E: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1 mg/day	Patch	0.025 mg/day patch twice weekly
Vaginal estrogen for systemic absorption (see separate vaginal estrogen table for atrophy treatments)			
Femring	E: 0.05 mg, 0.1 mg/day	Vaginal ring	Change every 3 months
Estrogen/testosterone combination			
Estratest	1.25 mg esterified estrogens + 2.5 mg methyltestosterone	Tablet	Daily
Estratest HS	0.625 mg esterified estrogens + 1.25 mg methyltestosterone	Tablet	Daily
Combined continuous estrogen/progestins			
Activella	1 mg E + 0.5 mg NE	PO tablet	Daily
Angeliq	1 mg E + 0.5 mg drospirenone	PO tablet	Daily
FemHRT	5 mcg EE + 1 mg NE	PO tablet	Daily
Prefest	1 mg E, 1 mg E + 0.09 mg N	PO tablet	Daily in order (alternates E × 3 days, E + N × 3 days)
Prempro	0.625 CEE + 2.5 mg MPA 0.625 CEE + 5.0 mg MPA	PO tablet	Daily
Climara Pro	0.045 mg E + 0.015 mg NE/day	Patch	Weekly
CombiPatch	0.05 mg E + 0.14 mg NE 0.05 mg E + 0.25 mg NE	Patch	Twice weekly
Combined sequential			
Premphase	0.625 mg CEE × 14 days, then 0.625 CEE + 5 mg MPA × 14 days	PO tablet	Take daily in order
Vivelle/ CombiPatch	0.05 E × 14 days, then 0.05 mg E + 0.14 mg NE OR 0.05 mg E + 0.25 mg NE × 14 days	Patch	Apply Vivelle twice weekly × 14 days, then CombiPatch twice weekly × 14 days
Oral progestins			
Amen, Cycrin, Provera, Curretab	MPA: 2.5 mg, 5 mg, 10 mg	Tablet	5–10 mg for 12 days/month with estrogen
Prometrium	Micronized progesterone: 100 mg, 200 mg	Tablet	200 mg daily × 12 days/month with estrogen
Aygestin	NE: 5 mg	Tablet	2.5–5 mg for at least 10 days each month

TABLE 24.11 Available Hormone Therapy Preparations *(Continued)*

Brand	Components and Strengths	Route	Recommended Starting Dose
Other progestins			
Prochieve	Micronized progesterone: 4%, 8%	Vaginal gel	1 applicator of 4 or 8% gel intravaginally every other day × 6 doses
Mirena	Levonorgestrel 20 mcg/day	Intrauterine system	Replace every 5 years

CE, conjugated estrogen; CEE, conjugated equine estrogen; E, estradiol; EE, ethinyl estradiol; N, norgestimate; MPA, medroxyprogesterone acetate; NE, norethindrone acetate.

Alternatives to daily or cyclic regimens have been investigated. To minimize bleeding frequency and side effects from progesterone, a 14-day course of MPA administered every 3 months was tested.[172] This quarterly administration of MPA—given the first 14 days of every third calendar month—produced longer menses and a higher incidence of heavy menses and unscheduled bleeding. The study by Ettinger et al.[172] did find that this regimen is associated with endometrial hyperplasia in 1.5% of women after 1 year. In contrast to this study, a scheduled 5-year Scandinavian study using this approach had to be cancelled after 3 years because of rates of hyperplasia and one case of endometrial cancer.[173] For women and clinicians who choose to use the extended cycle approach, endometrial monitoring via periodic surveillance of the endometrium or annual endometrial biopsy may be necessary.

Finally, although more data is needed regarding use for this purpose, the levonorgestrel containing IUD shows promise as a locally acting progestational agent providing endometrial protection for the uterus in postmenopausal women taking estrogen.[174] When initiating treatment for vasomotor symptoms prior to the cessation of menses, lower dose oral contraceptives or cyclic HT will usually result in more predictable bleeding.

Formulations and Routes of Administration

There are a variety of estrogen preparations that may be used for systemic therapy. The choice of estrogen therapy is based on patient preference, ease of use, and differences in rate of drug release and delivery site.

Both oral and transdermal vehicles are available for systemic estrogen administration. Oral estrogens are absorbed through the gastrointestinal trace and pass first through the liver, whereas transdermal products are absorbed directly into the bloodstream. Hence, oral estrogen results in a four- to five-fold higher concentration of estrogen in the hepatic portal system compared with transdermal estrogen. In addition, because of this "first pass" hepatic metabolism, much higher doses of estrogens are required orally. Transdermal agents may result in steadier therapeutic concentrations, with less individual variability.[175] Compared with oral estrogens, transdermal agents produce slightly attenuated but still significant decreases in LDL cholesterol and increases in HDL cholesterol. In contrast to oral agents, transdermal estrogens significantly lower triglyceride levels.[176] In comparison to oral estrogens, transdermal agents cause fewer alterations in the levels of thrombotic and anticoagulation factors, and overall, do not disturb the balance between these factors.[177] Several studies also suggest that high-sensitivity C-reactive protein levels are not elevated with transdermal estrogens as compared with oral agents.[177,178] Oral and transdermal routes of estrogen administration improve endothelial function to the same degree.[179] It is not clear that any of these metabolic changes are translated to fewer clinical events. Results from the Estrogen and Thromboembolism Risk Study suggest that oral estrogen therapy may increase the risk for venous thromboembolic events, whereas transdermal therapy does not.[180,181]

Other estrogen delivery options currently available in the United States for treatment of vasomotor symptoms include estradiol gel (Elestrin, EstroGel, Divigel), estradiol topical emulsion (Estrasorb), and estradiol transdermal mist (Evamist). These can be used alone in women who have had a hysterectomy or in combination with oral progestins in women with an intact uterus (see Table 24.11 for doses). Future studies, including the KEEPS study,[182] will provide more direct comparison between oral and the various transdermal estrogens risk/benefit profiles.

The recent Women's Heart, Osteoporosis, Progestin, and Estrogen (HOPE) Study was designed to look more closely at the effects of lower doses (0.45 mg CEE and 0.3 mg CEE in combination with either 2.5 mg or 1.5 mg MPA) of hormone therapy. The goal of the HOPE Study was to determine whether lower doses of CEE alone or with MPA in a continuous regimen could relieve vasomotor symptoms and increase BMD, while yielding an acceptable safety and side effect profile. The trials found that the increase in BMD achieved with combinations using 0.45 mg of CEE were very close to those achieved with standard doses.[183] For relief of vasomotor symptoms, the HOPE Study found that the lower doses of CEE are almost as effective as the standard 0.625-mg dose and that they are more effective when combined with a progestin. A 1.5-mg dose of MPA was as effective as the 2.5-mg dose.[184] Based on the 1-year portion of the study, the combined regimens of CEE and 1.5 mg of MPA used in this study effectively prevented the increased

risk of hyperplasia associated with unopposed estrogen. The administration of unopposed 0.3 mg of CEE was demonstrated to increase the risk of endometrial cancer and this increase correlated with the duration of use.[185] The HOPE trial demonstrated significant increases in HDL, decreases in LDL and total cholesterol, and modest increases of triglycerides with any of the lower doses of CEE with or without MPA.[186] The trial was too small to permit any conclusions regarding the incidence of thromboembolism.

Monitoring Estrogen Levels

Monitoring estrogen levels in women on estrogenic therapies is not an easy task. Clinical assays differ in their technique and quality, and the various agents available represent a diverse array of estrogenic compounds. These variations may impede the assay's ability to adequately reflect estrogenic activity. For example, women using conjugated equine estrogens will have very low levels of estradiol detected by even highly specific assays for estradiol. Ethinyl estradiol will not be "seen" by the antibodies used in immunoassays for estradiol; hence, levels cannot be measured in women using this as hormone therapy. In general, appropriate dosing for individual women is achieved by titration of dose for optimum symptom relief with minimum side effects. Monitoring serum levels is not recommended for most patients.

Measuring hormone levels is useful only in select populations of patients. If a woman continues to request increasing doses of estrogens for symptom relief, an assay may be able to demonstrate adequate blood levels (depending on the agent she is using). FSH levels cannot be used to measure or monitor estrogen response because FSH is not regulated solely by estrogen.

Gallbladder Disease

Although the epidemiologic evidence indicates that use of estrogen increases the risk of gallbladder disease, it does not appear to be clinically significant. The Nurse's Health Study indicated that oral estrogens may increase the risk 1.5- to 2-fold.[187] Other trials have indicated an increase in the risk of cholecystectomy in past and current users of estrogen therapy.[188] It has not been definitively proven that nonoral routes of administration are without adverse effects on the biliary system but lack of hepatic first pass with transdermal delivery systems makes it theoretically less likely.

Cardiovascular Disease

There is a great deal of evidence from basic science about the potential benefits of hormone therapy on cardiovascular disease. Estrogen therapy decreases LDL cholesterol, increases HDL cholesterol, and reduces lipoprotein-a. Oral estrogen increases triglyceride levels. Ovariectomized monkey model studies have demonstrated a significant reduction in atherosclerosis in monkeys treated with either estrogen alone or estrogen with progesterone.[189] Both oral and transdermal estrogen is associated with vasodilation and decreased peripheral resistance.[179]

Estrogen diminishes the decline in basal metabolic rate that begins at menopause and the tendency to increase central fat deposition—both of which are risk markers for cardiovascular disease.[190,191] Estrogen therapy is also associated with lower fasting insulin levels and a lower insulin response to glucose.[192]

Observational studies in the literature provide support for the assertion that hormone therapy is associated with a 50% reduction in the risk of CHD.[193,194] The 20-year follow-up in the Nurse's Health Study found a 39% reduction in age-adjusted relative risk for CHD (RR 0.61, 95% CI 0.52 to 0.71), with both 0.625 mg and 0.3 mg of conjugated equine estrogens.[195]

Criticism over these observational studies, including the invocation of the "healthy user" effect as a large bias was one of the main motivators for the design and implementation of the WHI Study. Currently, use of HT is not recommended for the prevention of CVD.

From the WHI and other trials, including secondary prevention trials, it is clear that hormone therapy is not an effective therapeutic intervention in established CHD.[196–199] The effect of HT on risk of CVD likely depends on if it is estrogen alone, or in combination with progesterone, and if it is initiated in proximity or distant to the menopausal transition.[200]

Venous Thromboembolic Events

Multiple studies have indicated that hormone therapy approximately doubles the risk of VTEs, most often in the first 2 years of therapy. A similar finding was noted in both arms of the WHI.[196,197] This risk appears to be reduced with the use of statins and low-dose aspirin, although it is not known if concurrent use of these agents will fully protect against the increased risk associated with hormone therapy.[201,202] In one French case-control study, there was a four-fold increase in the risk of VTE among users of oral estrogen but no increase in risk among transdermal users of estrogen.[203]

Cognition

On average, almost all cognitive functions decline with age, but there is a large amount of variability in this decline. Many women notice increasing difficulty with recall and concentration during the menopausal transition.[204] These changes are generally attributed to stress, changes in general health, and normal aging. Estrogen receptors, both alpha and beta, can be found throughout the brain, including in the cerebral cortex, forebrain, hippocampus, and cholinergic system.[205–208] Several studies have demonstrated an association of HT with improved scores on verbal tests of memory and

activates brain areas involved in memory, whereas other several studies have shown conflicting results.[209–214] For example, a large prospective cohort study of the Rancho Bernardo retirement community failed to demonstrate any benefit from HT on cognitive tests.[214] A meta-analysis of nine randomized clinical trials found that only symptomatic postmenopausal women benefit from hormonal therapy.[215] It is unclear if the addition of progesterone diminishes that beneficial effect.[216]

In the more recently published WHI Memory Study (WHIMS), the data reported that combination hormone therapy increased the risk of probable dementia in women 65 years of age and older and failed to prevent mild cognitive impairment in women.[217] It should be noted, however, that the duration of follow-up in WHIMS was short, the average age at enrollment in WHIMS was 72.3 years, and only one combination formulation was tested. In addition, the only statistically significant finding was increased vascular dementia (not AD) in women 75 years and older and in women who had been exposed to hormone therapy for only a short term.

In a prospective trial of a fairly homogenous population in Utah, there was a reduction in the risk of AD among hormone users but only with long-term (i.e., more than 10 years) treatment.[218] More research is needed to determine the effects of estrogen alone, estrogen plus progestin, and progestin alone on central nervous system function and aging. In addition, as with effects on CAD, timing of initiation of HT may play an important role in its effect of memory and development of dementia.

Breast Cancer

Because the greatest risk factor for breast cancer is a woman's age, most women are diagnosed after menopause. In a more recent reanalysis of data from more than 160,000 women, the relative risk of breast cancer in current and recent users of HT (estrogen, estrogen with progestin) for more than 5 years was 1.35 compared with nonusers (95% CI 1.21 to 1.49), and the risk increased with increasing duration of use. This increase in relative risk was greatest in women with lower body weights.[219] This increased relative risk amounts to two extra cases of breast cancer diagnosed by age 70 for every 1000 women using HT for 5 years. In the same study, it was also noted that current and recent users of hormone therapy had only localized disease and ever-users had less metastatic disease compared with never-users. Similar to results seen in other trials, there was no effect of family history of breast cancer.[219,220] A positive family history of breast cancer is not a contraindication to the use of hormone therapy.

A similar risk (RR 1.2 in ET users, RR 1.4 in HT users) was demonstrated in a recent large observational study and also in the estrogen-progestin arm of the WHI trial (RR 1.24, CI 1.01 to 1.54).[221] Interestingly, no increase in breast cancer was seen in treated women in the estrogen-only arm of the WHI.[197] The Million Women Study was done in the United Kingdom and used data from questionnaires received from 1,084,110 women between 1996 and 2001. No increase in breast cancer risk was noted in past users, regardless of length of time since discontinuation and regardless of duration of use. The Million Women Study did demonstrate an increase in relative risk for breast cancer for current users (estrogen only RR 1.3, 95% CI 1.22 to 1.38, and estrogen plus progestin RR 2.00, 95% CI 1.91 to 2.09) and noted an increase in risk with increasing duration of use.[222] There are many criticisms of the Million Women Study, including many differences between users and nonusers, establishment of hormone use at entry only, an average time to breast cancer diagnosis of only 1.2 years, and average time to death of only 1.7 years.

No definite cause and effect between HT and breast cancer has been established. It is not clear from the many studies whether the use of postmenopausal HT initiates the development of new breast cancers, if these results reflect an impact on pre-existing but undetected tumors, or if it allows detection of a breast cancer without affecting it progression. Interestingly, the breast cancers diagnosed in HT users tend to be less aggressive, associated with a better prognosis and decreased mortality than in women not taking HT.[223–225] It has been hypothesized that this is due to increased surveillance and earlier detection, but it may also result from an effect on pre-existing tumors so they become evident at less virulent and less aggressive stages.

Endometrial Cancer

Uterine cancer is the leading gynecologic cancer affecting women in the United States and accounts for 2% of cancer-related deaths in women.[226] It has been shown that unopposed estrogen treatment in women with an intact uterus substantially increases the risk of developing endometrial cancer.[227] The risk of endometrial cancer rises with higher unopposed estrogen doses, longer treatment duration, and lingers for up to 10 years after the estrogen is discontinued. The incidence can range from 20% after 1 year of unopposed therapy to up to 62% after 3 years of unopposed estrogen use.[228] According to the PEPI trial, estrogen therapy increased the risk by 34%, and a more recent meta-analysis found that 10 years of unopposed estrogen increased the risk ten-fold.[229,230] Although there may be conflicting results regarding the risks or benefits associated with estrogen therapy for many other conditions, an increase in endometrial cancer associated with the use of standard doses of estrogen therapy alone has been reproduced in study after study. The addition of either cyclic progestins for a minimum of 10 days a month or continuous progestins to estrogen eliminates this increased risk of endometrial cancer.[172,231–234] Most of the current evidence supports the use of a progestational agent for 12 to 14 days. Although estrogen-progestin therapy will not result

in an increased risk in endometrial cancer, it does not eliminate the risk for the development of this disease entirely. When clinically indicated, patients on estrogen and progestin regimens should be evaluated for endometrial pathology.

Other Cancers

There is conflicting data regarding the potential risk of ovarian cancer associated with HT. Several observational studies have been conducted with variable results spanning from a slightly increased risk with more than 10 years of estrogen use to no increased risk.[235–239] More recently, a cohort study of 44,271 postmenopausal women reported an increased risk of ovarian cancer in women who had used estrogen alone (RR 1.6, CI 1.2 to 2.0), especially with prolonged use. Conversely, combination HT was not associated with an elevated ovarian cancer risk in a separate study.[240] Although the WHI concluded that combined estrogen-progestin treatment may increase the risk of ovarian cancer, the small numbers in this trial limits its statistical power to make any definitive conclusions.[234]

Colorectal cancer is the third leading cause of cancer death in women and is more prevalent than cancer of the uterus or ovary.[226] HT appears to be protective against colorectal cancer in postmenopausal women. This has also been shown in multiple observational studies.[241–245] The effect seems to be greatest for current users and is not enhanced with increasing duration of use.[246] Estrogen appears to reduce the secretion and concentration of bile acids in the colon and may act directly on the colon by inhibiting the growth of human colon cancer cells.[242,246] The estrogen-progestin arm of the WHI reported a statistically significant reduced risk of colon cancer, although there were too few cases of rectal cancer to assess the impact of hormonal therapy on this disease.[247] The estrogen-only arm of the WHI did not show a difference in colorectal cancer rates.[197] In some studies, hormone therapy was associated with improved survival in women who had been diagnosed with colon cancer. In a study of 815 postmenopausal women diagnosed with colon cancer, Slattery and colleagues demonstrated that women who had ever used HT had a 40% lower probability of dying from colon cancer. Women who had used HT for at least 4 years had the lowest risk of dying of colon cancer.[248]

Although the association between cervical cancer and HT has not been studied extensively, it appears that use of hormonal therapy does not increase the risk of cervical cancer and may be somewhat protective.[250]

WITHDRAWAL OF HORMONE THERAPY/ ESTROGEN THERAPY

Since the release of the WHI data, clinical recommendations for the use of HT after the menopause have changed drastically. Several well-respected organizations currently recommend that HT be used for relief of life-limiting symptoms at the lowest dose for the shortest time possible.[251,252] Recent data seem to indicate that timing of initiation (i.e., closer to menopause) impacts long-term outcomes, especially regarding risk of CVD. It is not clear what effect, if any, duration of use has on CVD risk when treatment is initiated close to the menopausal transition. The preponderance of data would suggest, at least for combination HT, that breast cancer risk is elevated in HT users over nonusers. Weighing risks and benefits for each individual woman is a crucial component of the ongoing care of women who elect to use HT. Many women wish to discontinue HT because of fears regarding long-term risks. However, the symptoms which prompted initiation of treatment recur at least 50% of the time when treatment is discontinued. Studies to date have not demonstrated a method for discontinuation that decreases recurrence of symptoms.[253–255] Periodic re-evaluation of treatment goals and patient risk factors helps guide women and their caregivers in decision making. Lowering of dose and/or discontinuation of treatment needs to be undertaken in the context of the rest of each individual woman's life. Anticipatory guidance regarding the temporary nature of recurrence of symptoms and choice of the least stressful timing for decreasing and/or discontinuing treatment may aid in success in efforts to arrive at "the lowest dose for the shortest time possible." The effective management of HT requires an active partnership between the individual woman and her caregiver.

CONCLUSION

The transition to menopause marks a critical time in a woman's life. Profound but gradual changes occur that have long-term implications for the overall health, reproduction, and quality of life. Understanding of these changes and the available treatments to maximize women's health and well-being continues to evolve. Attention to lifestyle, health risk factors and health maintenance is crucial in optimizing health and quality of life in peri- and postmenopausal women. Currently, replacement of reproductive hormones is felt to be indicated only for relief of vasomotor and atrophy symptoms and should be used at the lowest dose for the shortest time. Treatment plans should be consistent with an individual woman's goals and tolerance of risk. While hormone replacement is one of the most studied medications ever, understanding of the effects of timing, route, and dosage of various hormonal regimens on long-term risks and benefits continues to evolve. In addition, alternative treatments for relief of menopausal symptoms and prevention and treatment strategies for diseases common to aging such as osteoporosis, CVD, and AD continue to evolve.

CLINICAL NOTES

- The menopausal transition is characterized by variable menstrual cycles and an elevated FSH.
- Menopause occurs after 12 months of amenorrhea, and postmenopause is the period from menopause until death.
- Once pathology has been excluded, bothersome irregular vaginal bleeding from anovulation in perimenopausal patients, especially if accompanied by vasomotor symptoms, can be treated with combined oral contraceptives as long as no contraindication exists.
- HT effectively treats vasomotor symptoms, genitourinary atrophy symptoms, skin aging, and may improve sexual functioning.
- Although HT improves cardiac risk factors, it is not currently thought to be beneficial for the prevention of CVD in women more than 10 years out from the menopause transition.
- The effect of combined HT on a newly menopausal woman appears to be neither cardioprotective nor cardio adverse.
- Oral HT increases the risk of stroke and VTE.
  - There is sufficient evidence to confirm that the effect of transdermal estrogen preparations on CVD, stroke, and VTE risk are different from that of oral administration.
- Bisphosphonates are currently the first-line therapies for the treatment of osteoporosis in postmenopausal women. SERMs also are an option for treatment of osteoporosis in postmenopausal women.
  - HT and SERMs may be indicated for the prevention of osteoporosis in selected at-risk women after menopause.
- SERMs also have been shown to decrease risk developing breast cancer in higher risk women.
- SERMs are not effective treatment for menopausal symptoms.
- HT is associated with a small increased risk of breast cancer which becomes evident after 4 years of use. These cancers appear to be less aggressive and are associated with a decreased mortality compared with cancers in women not taking HT.
- Unopposed estrogen therapy increases the risk of endometrial cancer. However, the addition of progestin reverses this risk.
- HT should be used primarily for the treatment of menopausal symptoms and prevention or treatment of osteoporosis. Treatment should be individualized, depending on the patient's symptoms and risk factors. Efforts should be made to treat symptoms with the lowest dose and treatment should be periodically reevaluated and used for the shortest time possible.
  - The optimum method for withdrawing HT has not been established. Efforts to discontinuation/reduction of HT must be individualized and take into account a woman's individual goals, risk factors, and symptoms.

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CHAPTER 25

Lesbian, Gay, Bisexual, and Transgender Women's Health

Kirsten M. Smith and Olivia Bolles

Lesbian and bisexual women are part of our patient population. It is estimated that 1.4 to 5.0% of the female population in the United States have engaged in same-sex behavior with other women.[1,2] In the year 2000 census in the United States, "same-sex" households were found in over 99% of counties, with the highest prevalence in urban areas, where they ranged from 5 to 7% of households.[3] This translates to 1.9 to 6.8 million women when using U.S. Census Bureau estimates from July 2009 (age 10 years and older for a total of 135,070,678 females in the United States).[4]

How does one define "lesbian"? Human sexuality has three components: attraction, behavior, and identity. So this means a lesbian may be defined as a woman who is attracted to a woman, a woman who engages in sexual behavior with a woman, and/or a woman who self-identifies as lesbian. A bisexual woman may be a woman who has attraction for and/or engages in sexual behavior with both men and women. Surveys of self-identified lesbians show a wide range of sexual behaviors (e.g., celibacy, heterosexuality, bisexuality, homosexuality). Behavior is not always concordant with self-identification and may change, sometimes frequently, over time. For example, a self-identified lesbian may also be attracted to, and engage in, sex with transgender individuals. Because of this fluidity in sexual behavior, it is advisable to discuss sexual behavior history with every patient at each visit. These discussions may be easier if patients are told that questions relating to sexual identity and behavior are asked of everyone because these issues have direct, and indirect, relevance to health care and preventive medicine decisions.

As alluded to above, human sexual orientation exists as a continuum ranging from solely heterosexual to solely homosexual. Although the mechanisms for the development of a particular sexual orientation are unclear, current literature and most scholars in the field state that sexual orientation is not a choice. Sexual orientation is likely determined by a combination of genetic, hormonal, and environmental influences.[5,6]

Lesbian and bisexual women are at risk for the same kinds of health problems as other women; their sexual orientation alone does not put them at higher risk for any particular health issues per se. However, their health risks may be influenced in unique ways, that is, differential risks for disease may arise because of specific behaviors that may be more common in this population. According to large-scale national surveys, women who have sex with women are more likely to smoke and drink alcohol, have a high body mass index (BMI), be nulliparous or of low parity, and have fewer preventive health screenings than heterosexual women[7,8]; they are less likely to have used oral contraceptives or to have breastfed. These characteristics constitute high-risk factors predisposing to colon, lung, endometrial, ovarian, and breast cancer, as well as cardiovascular disease and diabetes.

There are also differences in the stresses to which they are exposed that have a psychosocial impact. Although homosexuality is a normal variation of human sexual and emotional expression, lesbian women frequently endure prejudice and discrimination in both their public and private lives across their lifespan.

Lesbian and bisexual women are confronted with many barriers to quality health care, including fears of disclosure and the subsequent homophobic and heterosexist attitudes among health care providers.[9–11] Homophobia is defined as the irrational fear of and negative attitude toward homosexual people. In the United States, there are two particularly prominent influences that foster antihomosexual attitudes—religious fundamentalism and heterosexism. Heterosexism is the belief in the moral superiority of institutions and practices associated with heterosexuality.[12,13] Heterosexism not only exerts external pressures from societal expectations, it also has internal influences. It may instill shame in lesbian, gay, and bisexual individuals, causing them to internalize the homophobia that is directed toward them by society.

BARRIERS TO CARE

Interaction with the health care system may be inherently different for lesbian women. The Institute of Medicine (IOM) defines three primary types of barriers when considering access to health care. These are (a) structural, (b) financial, and (c) personal and cultural barriers. Potential structural barriers include difficulty in accessing needed services, difficulty in finding and choosing a lesbian-friendly health care provider, lack

of health insurance coverage for members of lesbian households, and the lack of legal recognition of partners. Financial barriers exist for lesbian and bisexual women just as they do for heterosexual women—many women do not receive health care simply because it is unaffordable. They may lack health care insurance coverage and may have lower overall incomes.[14] Personal and cultural barriers that affect access to health care include the lack of cultural competency among health care providers, the fear of disclosure to providers, and the lack of lesbian focus in preventive and other health care. Many health care providers and many lesbians have misconceptions. For example, there are health care providers and lesbian women who believe lesbians do not need regular Pap tests or routine gynecologic care and that lesbian women are not at risk for sexually transmitted infections, including HIV.[15]

Cultural competency can be defined as a set of congruent behaviors, attitudes, and policies that enable a system or group to work effectively in cross-cultural situations. In health care settings, it is a comprehensive system of clinical practices, standards of care, management policies, and institutional philosophy that provides and optimizes health care by integrating and being responsive to the cultural factors that influence the attitudes and behaviors of every patient.[16,17] Cultural competency generally refers to the provision of services to differing ethnic or racial groups; however, it effectively encompasses the skills that are required to provide comprehensive care to lesbian and bisexual patients.[15]

Many lesbian and bisexual patients do not reveal their sexual orientation to health care providers. It has been reported that 53 to 72% of lesbians do not disclose their sexual orientation to physicians at the time they seek medical care.[18,19] Lesbian and bisexual women report and fear negative experiences with health care providers, including a reluctance/refusal to treat, negative comments during the patient–provider encounter, and rough handling during examination.[19,20]

In order to help establish a good patient–provider relationship, the office setting should be perceived as welcoming and nonjudgmental. The administrative and clinical office staff should be culturally competent. There should be clear and understood expectations for respecting patient confidentiality. Registration forms and questionnaires should use inclusive language. They should include terms that recognize the patient's significant relationships. For example, instead of simply asking if the patient is single, married, separated, widowed or divorced, include options such as "have a significant other" or "live with a domestic partner." A nondiscrimination policy can be displayed in the waiting area that includes sexual orientation and gender identity. It is also helpful to have reading materials available and posters/pictures that are inclusive of lesbians; these can be placed in the waiting areas, bathrooms, and/or exam rooms (Fig. 25.1).[21]

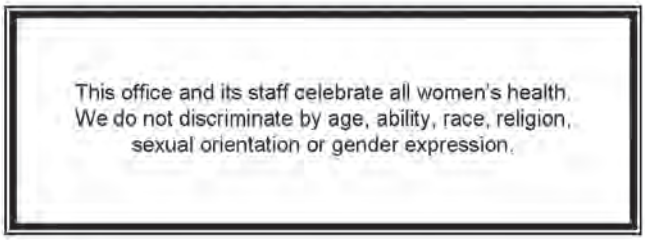

FIGURE 25.1 Nondiscrimination policy. (From O'Hanlan K. Health policy considerations for our sexual minority patients. *Obstet Gynecol*. 2006; 107:709–714.)

SEXUALLY TRANSMITTED INFECTIONS

It is important to consider screening lesbian and bisexual women for sexually transmitted infections (STIs) if their sexual behavior places them at risk. Most lesbians have been sexually active with men at some point in their lives. Approximately 80% of lesbians report having had sex with men in their lifetime and 21 to 30% report having sex with men in the past 1 to 5 years.[14] Although the overall incidence of vaginitis and STIs appears to be quite low in the lesbian population, all types of infections have been reported in lesbian and bisexual women and should be part of the differential diagnosis for vaginal discharge and pelvic pain.[22,23] STIs can be transmitted by exclusive lesbian sexual activity, although exclusive lesbian sexual activity is associated with the lowest rates of infection. Bisexual women are more likely to contract an STI than women with exclusive sexual activity with other women.[24,25]

Infectious agents can be transmitted between women through sexual behaviors resulting in the exchange of vaginal secretions on hands or objects, for example, finger-to-vagina contact, genital-to-genital contact, or sharing objects (sex toys) without condom use or cleaning between partners. Sex toys and fingers can also transmit bacteria from the anal region to the vagina.

Bacterial Vaginosis

Bacterial vaginosis (BV) is a condition characterized by overgrowth of anaerobic flora relative to the normal protective lactobacilli in the vagina. It may produce a vaginal discharge that may or may not have a fishy odor and it may cause vaginal and vulvar irritation. BV is commonly found among women who have sex with women and frequently occurs in both members of monogamous lesbian couples.[26] It has been identified in 25 to 52% of women who have sex with women.[26–28] One study found the prevalence of BV among lesbians to be 28.7%, and 72.7% of the patients' monogamous partners were concordant for BV. BV has been associated with receptive vaginal sex (penetration with fingers, a penis, or sex toy), receptive oral sex, a higher lifetime number of female sex partners, failure to always clean an insertive sex toy before use, and oral–anal sex with female partners.[26–30]

Herpes Simplex Virus

Transmission of herpes simplex virus (HSV) types 1 and 2 occurs with direct skin and mucous membrane contact. HSV transmission has been reported in women who have sex with women.[31] One study reported HSV among 7.4% of screened lesbians.[32] Marrazzo[31] examined the prevalence of HSV infection in 392 women who reported having sex with a woman in the preceding year, and HSV-1 and HSV-2 antibodies were measured by Western blot. HSV-1 antibodies were detected in 46% and HSV-2 antibodies were detected in 8% of study participants.[31] Transmission of herpes between women, from the mouth to the genital area, has been documented.[33] Because the virus can be transmitted even when no lesions are present, genital–genital, oral–genital, and digital–genital contact should involve latex barriers and couples should abstain from sex during HSV outbreaks. This is one of the most difficult areas to address when speaking to a lesbian individual/couple. If there are frequent oral and/or genital outbreaks, antiviral suppressive therapy should be discussed. Measures to prevent oral–genital transmission should be reviewed. Latex barriers can include condoms that have been cut open lengthwise, gloves that have been cut open, and dental dams. Plastic wrap may be used, although there is no data to support its effectiveness.

Human Papillomavirus

Seventy-five percent of sexually active adults in the United States demonstrate clinical or serologic evidence of genital human papillomavirus (HPV) infection.[34] The prevalence of HPV, including high oncogenic risk HPV, in women who have sex with women has been reported to be 13 to 30%, and the prevalence of HPV in women who have only had sex with women has been reported to be 6 to 19%.[35,36] HPV can be transmitted from woman to woman by skin-to-skin or skin-to-mucosa contact. The prevalence of HPV DNA by polymerase chain reaction (PCR) was strongly associated with more recent sex with men, higher lifetime number of male partners, and current cigarette smoking.[35,36] Marrazzo[31] also reports that the women who had never had sex with men were less likely to have ever received a pelvic examination, received their first Pap test at a later age, and had less frequent Pap tests than women who also reported a history of sex with men.[35]

Transmission of HPV may occur through direct genital-genital contact, digital-vaginal contact, and digital-anal contact. Genital HPV types have been identified on human fingers.[37] HPV may also be transmitted through the use of shared sex toys.[36]

Cervical dysplasia occurs in less than 3% of lesbians.[32] Although the risk for cervical dysplasia is increased with a history of previous heterosexual activity, high-grade squamous intraepithelial lesions have been identified in lesbian women who have no history of having sex with men.[38,39] Routine Pap testing for lesbians and bisexual women is recommended regardless of current type of sexual activity.[39,40] According to the current American College of Obstetricians and Gynecologists (ACOG) guidelines, cervical cancer screening should begin at age 21 years, regardless of timing of first sexual intercourse. Screening is recommended every 2 years for women between the ages of 21 and 29 years and can be performed with either conventional or liquid-based cytology. Women who are age 30 years and older, who have had three consecutive cervical cytology test results that are negative, should be screened once every 3 years. Women with certain risk factors may require more frequent screening, including those who have HIV, are immunosuppressed, have been exposed to diethylstilbestrol (DES) in utero, and have been treated for cervical intraepithelial neoplasia (CIN) 2, CIN 3, or cervical cancer.[41]

ACOG also recommends HPV vaccination, with the initial vaccination target being females between the ages of 11 and 12 years. Although obstetrician–gynecologists are not likely to care for many girls in this initial vaccination target group, they are critical to the widespread use of the vaccine for females aged 13 to 26 years. During a health care visit with a girl or woman in the age range for vaccination, an assessment of the patient's HPV vaccine status should be conducted and documented in the patient record.[42]

Chlamydia and Gonorrhea

Chlamydia and gonorrhea are transmitted to the vagina or rectum by contact with infected genital fluids. A survey of 2345 women (1921 lesbians and 424 bisexual women) revealed that bisexual women were more likely to report a gonorrhea infection, 7.8% versus 3.0% of the lesbian women.[43] Another survey, including 6935 lesbian women from across the United States, revealed that 17.2% had a lifetime history of sexually transmitted infection (STI). In this study, a lifetime history of chlamydia was reported in 4.6% of lesbians.[44] Bailey[45] reports a low prevalence of chlamydia (0.6%), pelvic inflammatory disease (0.3%), and gonorrhea (0.3%) among 708 lesbian and bisexual women attending a sexual health clinic in London—these infections were diagnosed only in women who had histories of having sex with men.

Syphilis

Syphilis is generally transmitted through heterosexual and male homosexual sexual activity,[43] although female-to-female transmission has been reported.[46] Bisexual behavior and exposure may allow transmission through oral contact and/or through shared sex toys.

Hepatitis A, B, and C

Acute viral hepatitis is characterized clinically by symptoms of malaise, nausea, poor appetite, vague abdominal pain, and jaundice. Hepatitis A is spread largely by the

fecal–oral route either in contaminated food or by oral–anal contact. Acute hepatitis A is invariably a self-limited infection; the virus can persist for months, but it does not lead to a chronic infection, chronic hepatitis, or cirrhosis.[47] Woman-to-woman transmission of hepatitis A has been reported.[48] Patients should avoid receptive oral–genital or oral–anal sex while infected.

Hepatitis B is spread predominantly by the parenteral route or by sexual contact. Chronic hepatitis B develops in 2 to 7% of adults infected with HBV. Chronic hepatitis B is a common cause of cirrhosis and an important cause of liver cancer.[47] Woman-to-woman transmission of hepatitis B has been reported.[40] Exchange of blood or body fluids, even by sharing a razor or toothbrush, may permit transmission. In addition to education and appropriate counseling, health care providers can offer vaccines for hepatitis A and hepatitis B.

Hepatitis C is primarily transmitted parenterally, although sexual and perinatal transmission does appear to occur. Injection drug users are at highest risk, accounting for more than 60% of cases. Prospective follow-up of spouses and sexual partners of patients with chronic hepatitis C shows the risk of sexual transmission to be low (less than 1% per year of exposure). Maternal–infant spread occurs in approximately 5% of cases.[47] Woman-to-woman transmission has not been studied.

Human Immunodeficiency Virus

HIV has been identified in menstrual blood, the white blood cells of vaginal secretions, and in saliva. HIV is transmissible during lesbian sexual activity—possibly more so during menses, episodes of vaginitis, or after traumatic sexual behavior.[14] In the February 2003 issue of *Clinical Infectious Diseases*, a likely case of HIV transmission between female partners was reported. An HIV-positive bisexual woman likely infected her lesbian partner by using sex toys so vigorously that her partner bled during intercourse. Genetic testing of the viral strains in the two women supported the suspicion that the bisexual woman had infected her partner. The bisexual woman was unaware that barrier protection was necessary when engaging in sexual activity with a woman partner.[49] There are other cases of suspected woman-to-woman sexual transmission of HIV.[50–52] There are also several studies that suggest considerable HIV risk behavior among some lesbian and bisexual women.[53–56] In a study of female STI clinic patients, Marrazzo[31] reports that when compared to women who report sex only with men, women reporting sex with both men and women had more recent partners, sex with partners at high risk for HIV, injection drug and crack cocaine use, and exchange of sex for drugs or money. In addition, women reporting sex exclusively with women more frequently reported prior sex with a bisexual man or an HIV-infected partner.[55,56]

HIV-related research on women who have sex with women has been scarce yet notable for its unexpected findings: (a) higher HIV seroprevalence rates among women who have sex with *both* women and men compared to their exclusively homosexual or heterosexual counterparts, (b) high levels of risk for HIV infection through unprotected sex with men and through injection drug use, and (c) risk for HIV infection of unknown magnitude owing to unprotected sex with women and artificial insemination with unscreened semen.[15]

Trichomoniasis

Trichomoniasis is a single-celled protozoan parasite. It can be identified in vaginal fluid and the vulvar glands. Several surveys report a prevalence of approximately 6% among women who have sex with women.[43,44,57] Woman-to-woman transmission has been clearly documented and is thought to occur by digital-genital contact and transfer of vaginal fluids.[58,59] If trichomoniasis is identified in a patient, her sexual partner(s) should be treated as well.[60]

SAFER SEX MEASURES

Safer sex measures should be discussed with lesbian and bisexual patients. Safer sex measures for women who exclusively have sex with women include barrier protection such as covering, with a new condom for each person, any sex toy that penetrates more than one person's vagina or anus; using a dental dam or latex barrier for oral–vaginal and oral–anal contact; and using latex or vinyl gloves and lubricant for any vaginal or anal penetration that may cause bleeding.[22,23] Proper cleansing of sex toys, such as dildos and vibrators, should take place not only before and after personal use but also before switching toys between partners when the same sex toy is shared. Dildos and vibrators can be cleaned with warm water and soap. Silicone can be cleaned by boiling for 2 to 3 minutes or in the dishwasher. If there are any visible genital lesions, physical contact should be avoided.[33] Additional safer sex measures for women who also have sex with men include always using a condom during vaginal or anal sex and always using a condom during fellatio (oral–penile contact).

DEMOGRAPHICS

Surveys of lesbian and bisexual women are generally based on convenience samples and nonprobability samples of women at lesbian social venues and organizations, counseling centers, and health clinics. These surveys report health behaviors such as tobacco, alcohol and drug use, obesity, and access to medical care. Survey data have suggested higher rates of nulliparity, higher BMI, less use of oral contraceptives, and higher rates of depression. In 1999, the IOM[15] published a report on

lesbian health—*Lesbian Health: Current Assessment and Directions for the Future*. The IOM[15] report made several recommendations for improving the knowledge base on lesbian health, each related to the need to fund and conduct research and disseminate information. Since the IOM report, several large population-based studies have been published. One of these studies was a subsample from the Women's Health Initiative (WHI).

The WHI was designed to investigate disease outcomes in older women; it was composed of three randomized clinical trials and a longitudinal observational study. Sexual orientation questions were embedded as one of many questions; response categories included "have never had sex," "sex with a woman or with women," "sex with a man or with men," "sex with both men and women," and "prefer not to answer." Valanis et al.[61] compared heterosexual and nonheterosexual women ages 50 to 79 years for specific demographic characteristics, psychosocial risk factors, screening practices, and other health-related behaviors. They found many of the same health behaviors—demographic and psychosocial risk factors—reported in the literature for their younger counterparts, despite higher socioeconomic status and access to health care.[61] This WHI subsample had 96,007 participants; this accounts for 59.3% of the final WHI sample. Of the 96,007, 2696 preferred not to answer, leaving the sample size for this study at 93,311. Breaking this down by sexual orientation, there were 90,578 heterosexual women, 740 bisexual women, 264 lifetime lesbian women (defined as sex only with women ever), and 309 adult lesbian women (defined as sex only with women after the age of 45 years). According to data collected from this WHI subsample, lesbian and bisexual women are more likely to have a higher BMI and be obese, use alcohol, and use tobacco (past and present). Lesbian and bisexual women are also less likely to have used oral contraceptives or have ever been pregnant.[61,62]

POTENTIAL IMPLICATIONS FOR LESBIAN/BISEXUAL HEALTH

Coronary Artery and Cerebrovascular Disease

Risk factors for coronary artery and cerebrovascular disease include smoking, obesity/excessive weight, high blood pressure, high cholesterol, physical inactivity, stress, and diabetes. Of these, smoking, obesity, and stress are potential demographic risk factors for lesbian or bisexual patients. In light of the increased likelihood for these risk factors, it is particularly important during routine office visits to include counseling for weight control, the importance of regular exercise, and smoking cessation as appropriate.[22] The WHI subsample data showed a slightly lower prevalence of stroke and hypertension in lesbian and bisexual women but the highest rates of myocardial infarction. Specifically, among the WHI population, 4.3% of adult lesbian women (defined as women who had sex only with women after age 45 years) and 3.1% of lifetime lesbian women (sex with only women during their lives) experienced myocardial infarctions compared with only 2.0% of heterosexual women and 1.2% of bisexual women.[61] Other studies with large samples of women have found increased cardiovascular risk and heart disease among lesbian women as well.[7,63] Risk factors included higher rates of obesity, smoking, and alcohol use as well as less intake of fruits and vegetables.

Cancer

There are risk factors that place women at greater risk for certain cancers (Table 25.1). For most cancers, risk increases with age or because there is a family history of that particular cancer. There are behavioral factors that can increase the risk of cancer as well. Because lesbians tend to have higher rates of smoking, alcohol use, poor diet, greater BMI, less use of oral contraceptives, and lower likelihood of bearing children, it has been suggested that lesbians are at higher risk for breast cancer.[15] Cochran et al.[62] examined behavioral risk factors, cancer screening behaviors, and self-reported breast cancer histories from seven independently conducted surveys of 11,876 lesbian and bisexual women. There was no statistically significant difference in self-reported prevalence of breast cancer between the lesbian sample and U.S. estimates for women.[62] The WHI subsample revealed the age-standardized prevalence of breast cancer to be 4.9% of heterosexual women, 8.4% of bisexual women, 5.8% of lifetime lesbians (sex only with women ever), and 7.0% of adult lesbians (sex only with women after age 45 years).[61]

Less information is available for the prevalence of other cancers among lesbian women. With higher rates of smoking, there is increased risk of lung cancer. With a higher BMI and a high-fat diet, there is greater risk for colorectal, ovarian, and endometrial cancers. Because lesbians are less likely to have given birth and less likely to have used oral contraceptives, they may have greater risk for endometrial or ovarian cancer.[15]

TABLE 25.1 Cancer Risk Factors

	Age	Family Hx	Nulliparity	No OC Use	Obesity	High Fat Diet	Alcohol	Tobacco
Breast	*	*	*		*	*	*	*
Colon	*	*			*	*	*	*
Endometrial	*	*	*	*	*	*		
Ovarian	*	*	*	*	*	?		

Hx, history; OC, oral contraceptive.
*Potential demographic risk factors for lesbian/bisexual patients.
?Unclear if this is a risk factor.

Overweight and Obesity

In the WHI subsample, lesbian and bisexual women tended to be more overweight or obese.[61] By combining data from seven independently conducted surveys of lesbian and bisexual women (n = 11,876), Cochran et al.[62] revealed an overall obesity rate of 28% among lesbian and bisexual women. In a more recent study of 5979 respondents for the National Survey of Family Growth, lesbians had more than twice the odds of being overweight (OR 2.69) and obese (OR 2.47).[64]

Tobacco

According to data collected from a 1996 HMO health survey in which 8113 women responded to the sexual orientation question and 1.5% reported being lesbian or bisexual, lesbian and bisexual women younger than 50 years of age were more likely to smoke cigarettes than heterosexual women. Specifically, for the 20- to 34-year-old group, 33.3% of lesbian or bisexual women were current smokers compared with 13.2% of heterosexual women. For the 35- to 49-year-old group, 29.1% of lesbian or bisexual women were current smokers compared with 14.4% heterosexual women.[65] These results are comparable to other population-based research findings.[62,63,66]

Alcohol

In the same 1996 HMO Health Survey, lesbian or bisexual women aged 20 to 34 years had significantly higher rates of heavy drinking than heterosexual women. These rates decreased dramatically among 34- to 49-year-old lesbian or bisexual women. Specifically, 23.3% of lesbian or bisexual women aged 20 to 34 years reported heavy drinking compared with 6.0% of heterosexual women in that age group. For 35- to 49-year-olds, this difference decreased substantially, but lesbian or bisexual women still were more likely to be heavy drinkers (7.1% versus 2.7%).[65] None of the lesbian and bisexual women older than 50 years of age met criteria for heavy drinking. The overall pattern for alcohol use among lesbians and bisexual women were comparable to those reported in other population-based research.[62,63,66]

Illicit Drug Use

There are limited data about illicit drug use by lesbian and bisexual women. Precise incidence and prevalence rates of substance use and abuse are difficult to determine for several reasons: (a) reliable information on the size of the lesbian/gay/bisexual/transgender population is not available, (b) epidemiologic studies on drug abuse rarely ask about sexual orientation, and (c) research studies cannot be compared because of inconsistent methodologies (Substance Abuse and Mental Health Services Administration [SAMHSA]).[17] There are two studies worth mentioning. Both studies were of similar size: 190 U.S. lesbian survey respondents and 200 New Zealand lesbian survey respondents. The rates of marijuana use were 30.5 and 33.0% within the past year, respectively.[67,68] Use of cocaine within the past year was reported to be 7% in the 1994 U.S. survey.[67] In the New Zealand survey, use of recreational drugs other than alcohol or cannabis within the past year was 4.5%.[68] There are certain subpopulations of injection drug users who are women that report same-sex contact; women who use intravenous drugs *and* engage in sex with women report more unsafe injection and sexual behavior with both women and men than other female injection drug users.[54]

If the previously mentioned demographic information is accurate, lesbian and bisexual women would be expected to have higher lifetime rates of coronary heart disease; cerebrovascular disease; breast, colon, endometrial, lung, and ovarian cancer, as well as diabetes, hypertension, and emphysema. Behavior modification, such as smoking cessation, less alcohol consumption, maintaining a healthy weight and diet, and regular exercise, can lower the risk for these health conditions. It is, therefore, important to screen patients for these risk factors and counsel them appropriately.

Mental Health

"Coming out" or disclosure of sexual orientation has been shown to be a precursor to good mental health for lesbian and bisexual women.[69] The positive effects of coming out include an increased self-esteem, better psychological adjustment, greater satisfaction, and less depression or stress than that experienced by lesbian or bisexual women who have not disclosed their identity.[14,70]

Coming out may have negative consequences. Individuals may become the target of discrimination or violence. Some individuals may experience rejection or physical/verbal abuse by family members and/or peers. For those who experience it, the internalized psychosocial effects of homophobia can be profound and may include feelings of isolation, shame, diminished self-concept, and self-destructive behaviors and health habits.[69,71] One systematic review found that lesbian, gay, and bisexual people were at significantly higher risk of mental health disorders, for example, depression, anxiety, and suicidal ideation, as well as substance abuse/misuse and deliberate self-harm, compared to heterosexual people.[72] In the same study, lesbian and bisexual women were at particularly high risk of substance dependence.

Questionnaire data collected from 2259 Sacramento area lesbians, gay men, and bisexuals (1170 women, 1089 men) revealed that one out of five women were victimized because of sexual orientation and one out of four men were victimized because of their sexual orientation. When compared with other recent crime victims, lesbian and gay hate crime survivors had more symptoms of depression, anger, anxiety and posttraumatic stress.[73]

Multiple studies have shown greater vulnerability to depressive distress and anxiety for lesbian and bisexual women.[7,61,65,74,75] Stress effects are magnified for those subject to multiple forms of discrimination. Lesbians who are also members of racial or ethnic minority groups are at particular risk for stress-induced depression.[76]

In the WHI subsample, lesbian and bisexual women were more likely than heterosexual women to be depressed. Specifically, the depression rate for the heterosexual group was 11.1% compared to rates of 15.0, 15.4, and 16.5% in the adult lesbian (sex only with women after age 45 years), in the bisexual group, and in the lifetime lesbian (sex only with women ever) group, respectively.[61]

In the National Comorbidity Survey, which was a population-based survey of 5877 individuals aged 15 to 54 years, 1.5% of women reported same-sex behavior. Results of this survey revealed statistically significant differences between women in the same-sex behavior and opposite-sex behavior subsamples in major depression (34.5% versus 12.9%), simple phobia (25.0% versus 13.3%), and posttraumatic stress (20.9% versus 5.9%).[74]

In the same National Comorbidity Survey, the prevalence of suicidal thoughts was higher in the same-sex behavior subsample than in the opposite-sex behavior subsample (13.9% versus 3.9%). And the prevalence of suicidal plans among women with same-sex behavior was higher, 15.2% versus 4.8% of women in the opposite-sex behavior subsample.[74]

Intimate Partner Violence

The National Institute of Justice and the Centers for Disease Control and Prevention jointly sponsored a national representative telephone survey in order to further understanding of violence against women in the United States. This National Violence Against Women survey interviewed 8000 women in the United States. One percent of women reported living with a same-sex intimate partner at least once in their lifetime. Eleven percent of these women reported being raped, physically assaulted, or stalked by a female partner, whereas almost 22% of women who had married or lived with a male partner reported these types of violence by a husband or male cohabitant.[77] Although these findings suggest that lesbians are at less risk for intimate partner violence, violence still may occur in same-sex relationships. Health care providers should screen all patients for domestic violence.

LIFESPAN ISSUES: HEALTH CONCERNS FOR THE LESBIAN AND BISEXUAL ADOLESCENT

Development of sexual identity is thought to begin around age 10 years and continues through adulthood. Data support that the development of sexuality involves a process that parallels the physical events of the Tanner stages.[71] Health care providers should use anticipatory guidance in caring for the adolescent patient and should be able to provide accurate and nonjudgmental information in a confidential manner. Giving evidence of support and acceptance to adolescents questioning their sexual orientation can be very important as can the provision of information and resources regarding gay, lesbian, and bisexual issues to all interested adolescents.[5]

Confusion about sexual orientation is not unusual during adolescence. Same-sex activity is not synonymous with sexual orientation. The overall goal in caring for adolescents who are or who think they might be gay or lesbian is to promote normal adolescent development, social and emotional well-being, and physical health.[78] Counseling may be helpful for youth who are questioning their sexuality, but therapy directed specifically at changing sexual orientation is contraindicated. It can provoke guilt and anxiety while having no demonstrated potential for achieving changes in orientation.[79] When counseling an adolescent about sexual activity, it is important to discuss abstinence, the importance of limiting the number of sexual partners, and safer sex measures, regardless of her reported sexual behavior.[5,80,81]

Prevalence

Results of a survey of more than 34,000 Minnesota adolescents revealed that 10.7% of high school students, both male and female, between the ages of 12 and 20 years were "unsure" of their sexual orientation; 4.5% of students reported homosexual attraction; and 1.1% of girls (and 1.5% of boys) described themselves as bisexual or homosexual.[82]

Sexual Activity and Pregnancy

Some homosexual adolescent patients engage in promiscuous heterosexual activity in an attempt to prove they are not homosexual. Young women who have sex with other females are especially likely to engage in unprotected sex with both male and female partners.[83,84] Although there is little research on heterosexual behavior in lesbian adolescents, a study of more than 36,000 public school students found that lesbian and bisexual adolescents had similar frequencies of intercourse when compared to their heterosexual peers (33% versus 29%) but a higher rate of pregnancy (12% versus 5%).[84]

Substance Use and Abuse

In the 1993 and 1995 Massachusetts Youth Risk Behavior Surveys (YRBS), youth with same-sex sexual behavior were significantly more likely to use tobacco, alcohol, marijuana, cocaine, and other illegal drugs.[85,86] Results of the 1995 Massachusetts YRBS showed that self-identified lesbian, gay, and bisexual youth were more likely than their peers to begin smoking cigarettes and using marijuana and alcohol before the age of 13 years,

to have higher lifetime rates of crack/cocaine use, and to report more recent use of tobacco.[85]

The National Longitudinal Study of Adolescent Health (Add Health) surveyed more than 20,000 adolescents in grades 7 through 12. Data from the Add Health study revealed bisexual adolescents to be at highest risk for substance use. Specifically, bisexual adolescent females used tobacco more, were more likely to consume alcohol alone, and were more likely to use marijuana and other drugs than those with same-sex only relationships.[87]

Homeless Adolescents

Studies assessing the sexual orientations of homeless adolescents have shown that 11 to 37% identify as gay or lesbian.[88–90] In one study, when compared with homeless heterosexual adolescents, homeless gay/lesbian/bisexual/transgender (GLBT) youth reported higher rates of addictive substance use. They also reported more frequent departures from home, higher levels of physical and sexual victimization, riskier sexual behavior, and more psychopathology. This study consisted of 375 youths (ages 13 to 21 years), 84 of whom (22.4%) were identified as part of a sexual minority (71 bisexual, 4 exclusively lesbian, 8 exclusively gay, and 1 transgender).[88] Many of the youth who are homeless leave home because of conflicts with parents over their sexual orientation.[91]

Violence

In the 1993 and 1995 Massachusetts YRBS, youth with same-sex sexual behavior reported higher frequencies of being threatened or injured with a weapon at school, being involved in physical fights, or having injuries from fighting requiring medical attention.[85,86] These students were also more likely to report weapon and gun carrying.[85] Violence because of their orientation can confer posttraumatic emotional sequelae, including depression, diminished self-esteem, and suicidal thoughts.[73,92,93]

Data from the Add Health study also suggests that youth with same-sex and both sex attractions are at greater risk for experiencing and witnessing violence when compared to heterosexual peers. The study also reported that youth with same-sex attraction are more likely than their peers to perpetrate extreme forms of violence against others (using a gun or a knife). This may be generated by feelings of fear and the need for self-defense.[94]

Mental Health

In terms of adolescent mental health issues, openly homosexual students are often subjected to physical and verbal abuse at school.[85] This may increase school avoidance behavior. In addition, rejection from society, family members, and peers may lead to isolation, runaway behavior, depression, suicide, substance abuse, and school or job failure.[71]

There is an association between adolescent sexual orientation and suicidal thoughts and behaviors. Youth with same-sex orientation are more than two times more likely than heterosexual peers of the same sex to attempt suicide. Youth with same-sex orientation score higher on several of the critical adolescent suicide risk factors. Specifically, they are more likely than heterosexual peers of the same sex to feel hopeless and depressed, to abuse alcohol, and to have experienced an attempted suicide by a family member or friend.[95]

LIFESPAN ISSUES: PREGNANCY AND PARENTING

According to data from the WHI, the pregnancy rate among heterosexual women was 92.4%. For bisexual women, the pregnancy rate was 80.8%. Rates for lesbians varied by whether the person identified themselves as a lifetime lesbian, meaning they have only had sex with women ever, or adult lesbian, meaning they have only had sex with women after age 45 years. For lifetime lesbians, the pregnancy rate was 35.0%. For adult lesbians, the pregnancy rate was 63.0%.[61]

There are many ways lesbians become parents—insemination with known or unknown donor sperm, children from previous heterosexual relationships, stepparenting, adoption, second parent adoption, and foster parenting. It has been estimated that between 6 and 14 million children in the United States have at least one parent who is lesbian or gay.[96]

Health care providers can provide preconception counseling, can serve as liaisons between lesbian/bisexual patients and sperm banks, can refer patients for assisted reproductive care, and can provide prenatal care and delivery. The American Society for Reproductive Medicine affirms the right of single, gay, and lesbian persons to have access to fertility services.[97] It is important to educate lesbian and bisexual patients about the importance of having documents to protect themselves and their families, for example, durable power of attorney, health proxies, second parent (or coparent) adoption, and custody issues in the event of separation, divorce, or death.[98]

A comprehensive review of multiple published studies of children raised in gay and lesbian households concluded that being raised in a household of this type does not influence a child's development of gender identity, sex-role behavior, sexual orientation, self-concept, locus of control, moral judgment, intelligence, or development of peer relationships. In addition, no differences have been found in the toy, game, activity, dress, or friendship preferences of boys or girls who have lesbian mothers, compared with those who have heterosexual mothers.[99–101] In a study comparing adolescent children in same-sex families to adolescents in opposite-sex families, there were no significant differences in psychosocial adjustment, school outcomes, and romantic relationships;

TABLE 25.2 Second or Coparent Adoption

- Protects child's rights to maintain continuing relationships with both parents
- Guarantees second parent's custody rights and responsibilities will be protected if first parent were to die or become incapacitated
- Protects second parent's rights to custody and visitation if couple separates
- Establishes requirement for child support in the event of parents' separation
- Ensures child's eligibility for health benefits from both parents
- Provides legal grounds for either parent to provide consent for medical care and to make education, health care, and other important decisions on behalf of the child
- Creates basis for financial security for children in the event of the death of either parent

the authors determined that it is the quality of the parenting that makes the difference in adolescent development and adjustment, rather than the parent's sexual orientation.[102]

Second Parent Adoption

Children born or adopted into families headed by partners who are of the same sex usually have only one biological or adoptive legal parent. The other partner in a parental role is called the "coparent" or "second parent." In 2002, the American Academy of Pediatrics released a statement on coparent or second parent adoption by same-sex parents. It states, "Children who are born to or adopted by 1 member of a same-sex couple deserve the security of 2 legally recognized parents. Therefore, the American Academy of Pediatrics supports legislative and legal efforts to provide the possibility of adoption of the child by the second parent or coparent in these families."[103]

Several other medical organizations, including the ACOG and the American Medical Association (AMA), support equal access for lesbians to coparenting and second parent adoption rights (Table 25.2).[98,104]

LIFESPAN ISSUES: AGING

According to UCLA's Williams Institute on Sexual Orientation and the Law, there are an estimated 1.5 million lesbian/gay/bisexual elders today in the United States, and this is anticipated to reach 3 million by 2030.[105] Lesbian, gay, bisexual, and transgender (LGBT) elders face three unique challenges that make successful aging more difficult. (The following information is taken from the March 2010 report "Improving the Lives of LGBT Older Adults," retrieved from the website www.sageusa.org.)

1. **The effects of social stigma and prejudice, past and present**
   Historical prejudice against today's LGBT elders has disrupted their lives, their connections to their families of origin, their chance to have and raise children, and their opportunities to earn a living and save for retirement. Many LGBT elders are reluctant to seek needed services and care from potentially hostile providers and are reluctant to reveal their identity to their heterosexual peers.
2. **Reliance on informal "families of choice" for social connections, care and support**
   Approximately 80% of long-term care in the United States is provided by family members.[106] LGBT elders are only half as likely as heterosexual elders to have close relations to call for help. This is because LGBT elders are often estranged from biological family. They are also two to three times as likely to be single, and greater than three times more likely to be childless, compared to heterosexual peers.[107–109] LGBT elders therefore often rely on friends and community members as their chosen family. This can cause problems because official policies, laws, and institutional regulations generally prioritize only legal and biological family and in many instances, deny resources and support to same-sex partners, families of choice, and other caregivers who do not fall into traditional categories.
3. **Unequal treatment under laws, programs and services**
   Many safety net programs are designed around the presumption of marriage. For example, Social Security provides extra benefits to spouses. Despite paying into Social Security in the same manner as their heterosexual peers, LGBT elders are not equally eligible for Social Security benefits. Committed same-sex couples are denied the substantial spousal and survivor benefits provided to heterosexual married couples. Lesbian couples receive an average of 31.5% less in Social Security when compared to heterosexual couples (Fig. 25.2).[105]

According to the Williams Institute, May 2009, senior lesbian couples have a higher rate of poverty than that of senior heterosexual couples, 9.1% versus 4.6%.[105] Age, poverty, and health issues can render the older lesbian nearly invisible. The tendency for lesbian seniors to go "back in the closet" is particularly pronounced in situations where they are most vulnerable—such as when accessing home health care or residing in assisted living or residential care facilities.[110]

LEGAL STATUS AND ITS HEALTH IMPACT

Civil marriage, according to the federal government, must be between a man and a woman. It confers legal recognition of the committed relationship between two people and grants 1138 federal statutory provisions as well as additional state protections, benefits, and responsibilities designed to support and protect family life.[111]

Civil union has a more limited scope than civil marriage. It confers state law–based benefits, protections, and responsibilities. Civil unions are not reciprocally recognized in most states and are not recognized by the federal government. Currently in the United States,

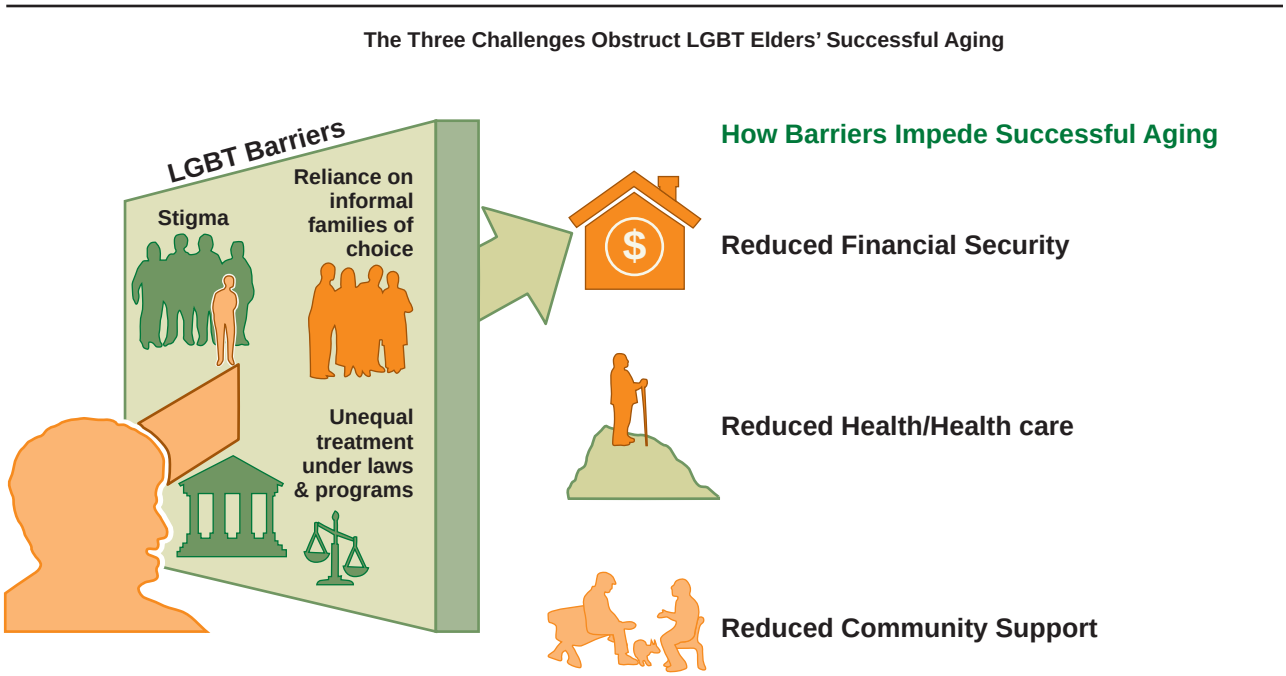

FIGURE 25.2 The challenges LGBT elders face create difficulties for them to age successfully and securely. (From LGBT Movement Advancement Project; Services and Advocacy for Gay, Lesbian, Bisexual and Transgender Elders. Improving the lives of LGBT older adults: snapshot report. http://www.lgbtagingcenter.org/resources/pdfs/ImprovingtheLivesofLGBTOlderAdultsSnapshot.pdf. Accessed December 5, 2013.)

same-sex marriage is available in some states, for example, Massachusetts (2004), Connecticut (2008), New Hampshire (2008), Iowa (2009), Vermont (2009), and Washington, DC (2010). Approximately 18,000 same-sex couples married in California in 2008. Then in November 2008, the voters in California voted to amend the California Constitution. The California Marriage Protection Act, also known as Proposition 8, states that "only marriage between a man and a woman is valid or recognized in California." At this time, same-sex couples are not able to marry in California; however, the state still recognizes the marriages that were granted to same-sex couples prior to the passage of Proposition 8.[112]

Domestic partnership is a legally recognized partnership between two individuals who may or may not be of the same sex. Domestic partnership does not provide the same rights, benefits, and protections as civil marriage or civil union and what is provided varies by jurisdiction.[113]

Legal recognition of the relationship between same-sex partners is important and affects the health and well-being of our lesbian and bisexual patients. Here are some examples of situations that have an interface between health care concerns and legal status of same sex-partners.

Legal Spouses

- Are considered next of kin for the purposes of hospital visits and emergency medical decisions
- Individually have the right to consent for medical treatment and health care decisions for their children
- May have better access to health insurance (coverage for spouse and children)
- When eligible for Family and Medical Leave Act (FMLA), may take leave to care for immediate family members (spouse, child, parent)
- When a legal spouse dies, the surviving spouse or legally recognized family member can sign for the release of the body from the hospital for funeral/disposition arrangements.

There are additional considerations. Legal recognition of same-sex partners and their families would also provide more financial protection. Financial security is intimately tied to access to health care: (a) Health insurance benefits to employees, their legal spouses, and children are considered benefits exempt from federal income tax. With Domestic Partner benefits, the employee pays for coverage with post-tax dollars and then must also pay tax on the employer's share of payment for the benefits as added income. (b) Legal spouses can file joint tax returns and are eligible for additional tax benefits and claims. (c) A legal spouse is eligible for the Social Security benefits of the deceased partner, can inherit retirement savings tax-free and can inherit a shared home, assets, and personal items in the absence of a will (Fig. 25.3).[41]

There are essential life-planning documents that are important for all individuals (Table 25.3). However, same-sex couples are more vulnerable and are left to piece together a patchwork of legal and financial documents in an attempt to protect themselves and their families.

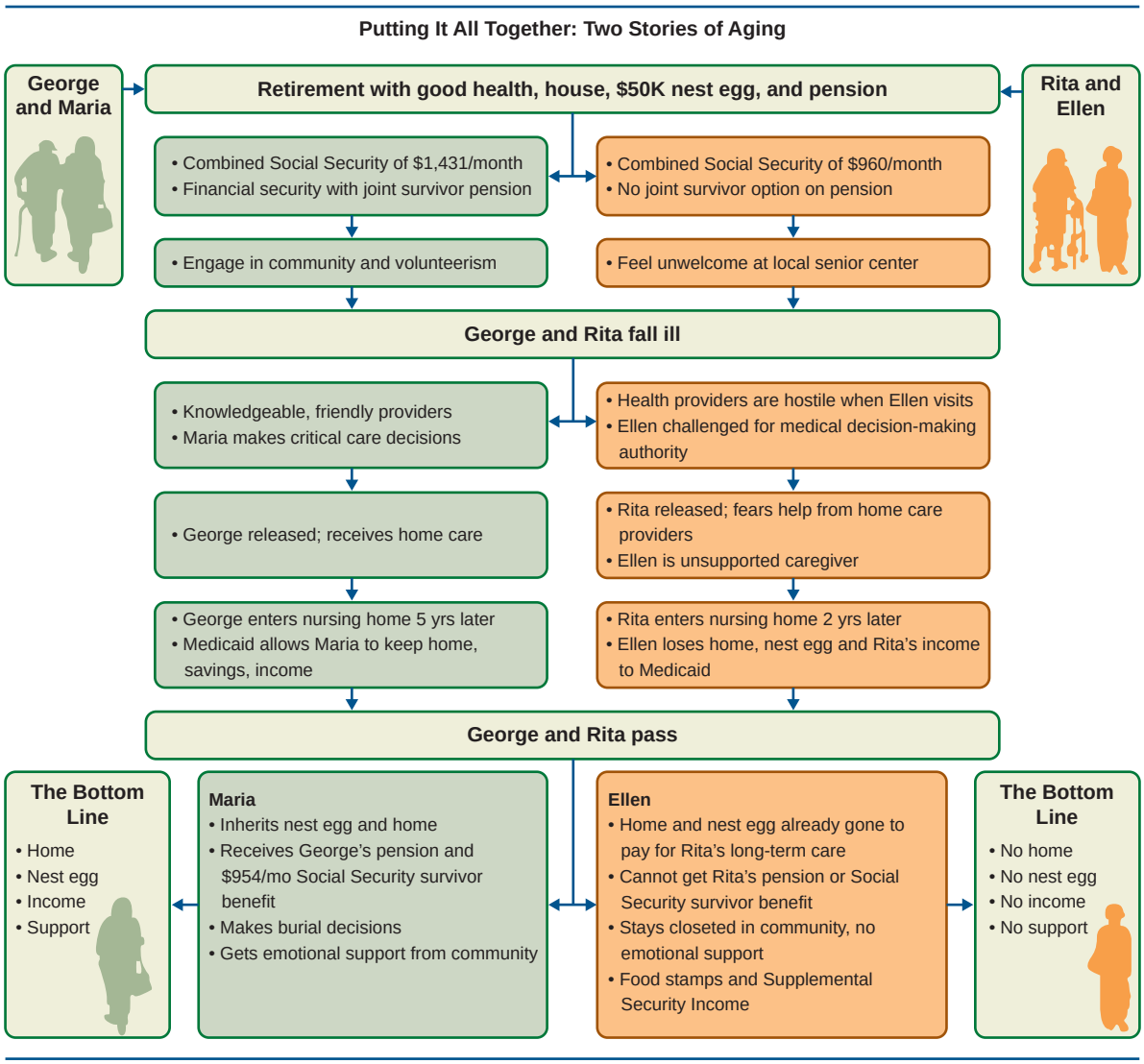

FIGURE 25.3 This illustrates the barriers LGBT couples face after retirement compared to heterosexual couples. (From LGBT Movement Advancement Project; Services and Advocacy for Gay, Lesbian, Bisexual and Transgender Elders. Improving the lives of LGBT older adults: snapshot report. http://www.lgbtagingcenter.org/resources/pdfs/ImprovingtheLivesofLGBTOlderAdultsSnapshot.pdf. Accessed December 5, 2013.)

TABLE 25.3 Essential Life Planning Documents

Last Will and Testament
- Ensures that property distribution wishes are recognized and legally enforceable
- Without a legal will that documents specific wishes, laws known as intestacy laws automatically dictate that the biological family will inherit all property and possessions.

Durable Power of Attorney
- Allows a person to appoint a trusted representative to act on his or her behalf in legal and financial matters

Living Will/Medical Directive/Advanced Directive
- Documentation of wishes regarding end-of-life treatment
- Guides the decisions that a person's agent or doctors make on his or her behalf

Health Care Proxy/Medical Power of Attorney/Durable Power of Attorney for Health Care
- Allows a person to appoint a trusted partner, friend, or family member to make health care decisions in the event that he or she becomes incapacitated due to illness or injury

PROFESSIONAL MEDICAL SOCIETIES AND THEIR GAY, LESBIAN, BISEXUAL, AND TRANSGENDER POLICIES

The American Medical Women's Association issued a position statement on lesbian health in 1993 encouraging national, state, and local legislation to end discrimination based on sexual orientation in housing, employment, marriage, tax, and child custody and adoption laws.[114] The American Psychological Association, the American Psychiatric Association, the American Psychoanalytic Association, and the National Association of Social Workers have issued policy statements supporting civil marriage for same-sex partners.[115–118] The American Academy of Pediatrics recognizes the advantages for children having two legally recognized parents; in 2002, they published their technical report in support of second parent adoption by same-sex

TABLE 25.4 What Can We Do as Health Care Providers?

- Educate our patients about the importance of having the proper legal documents for individual/family protection.
- Discuss the health care proxy and living will prior to admission to the hospital; the documents should be included in the patient's medical record.
- Include the name of the patient's partner on admission orders and give his or her permission to visit as a family member.
- Educate ourselves, our colleagues, our office staff, our residents, and medical students.
- Advocate for equitable and nondiscriminatory treatment for lesbian women and their families.

parents.[101] In 2006, the American Academy of Pediatrics endorsed civil marriage for same-sex couples.[111] In its report *Health Care Disparities in Same-Sex Partner Households*, the AMA recognizes that exclusion from civil marriage contributes to health care disparities affecting same-sex households; in this report, the AMA pledges to work to reduce health care disparities among members of same-sex households including minor children, as well as support measures providing same-sex households with the same rights and privileges to health care, health insurance, and survivor benefits, as afforded opposite-sex households.[119] The ACOG Committee Opinion, *Legal Status: Health Impact for Lesbian Couples*, endorses equitable treatment for lesbians and their families, "not only for direct health care needs but also for indirect health care issues, which includes the same legal protections afforded married couples" (Table 25.4).[41]

TRANSGENDERED INDIVIDUALS

Transgendered individuals have a strong desire to be the opposite gender and have significant discomfort with their assigned gender role. They believe they were born into a body with the wrong physical gender. It is not an issue of choice for them. It is also not an indication of their sexual orientation or sexual behavior; a transgendered individual may be heterosexual, homosexual, or bisexual.[120]

According to the definition of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM-IV*), transgenderism is not itself a mental disorder. There are four diagnostic criteria that have to be present for the diagnosis of gender identity disorder: (a) a strong and persistent cross-gender identification—manifested by stated desire to be the other sex, desire to live or be treated as the other sex, or the conviction that he or she has typical feelings and reactions of the other sex; (b) persistent discomfort with his or her gender, manifested by a preoccupation with getting rid of primary and secondary sex characteristics (requests for hormones, surgery, or other procedures to simulate the other sex); (c) the disturbance is not concurrent with a physical intersex condition; and (d) the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.[121]

Individuals who wish to change their gender may present in the office for gynecologic care. Health care providers can provide routine health maintenance and preventive care. In addition, for this population, the gynecologist can assist with treatment and/or refer to the appropriate consultants and provide valuable resources for education and support. Comprehensive care of transgendered patients requires a multidisciplinary approach and involves an array of medical, surgical, and behavioral health service providers. These patients are generally cared for in centers specializing in transgender/transsexual care. There are a variety of treatment options for patients with gender identity disorder. The World Professional Association for Transgender Health (WPATH), formerly the Henry Benjamin International Gender Dysphoria Association, has published standards of care for the treatment of transgendered individuals. Amongst other aspects of therapy, the WPATH standards of care describes triadic therapy, composed of a real-life experience in the desired gender role, hormones of the desired gender, and surgery to change the genitalia and other sex characteristics.

Transgendered individuals must be evaluated by a mental health professional and/or undergo extended psychotherapy prior to initiating any medical or surgical treatment. The mainstay of medical treatment of transgendered patients involves hormone therapy. Surgical treatment of these patients is broadly referred to as sex reassignment surgery. Surgical therapy may involve breast surgery, gonadectomy, genital reconstruction, or any combination thereof. General gynecologists are more likely to be involved in the medical management of these patients in addition to providing routine preventive health care. Gynecologists with specialized training in sex reassignment surgery are more likely to be involved in the surgical management of transgendered patients, although the general gynecologist may be involved in performing hysterectomies and/or oophorectomies in biological females seeking male reassignment.[122,123]

Medical therapy for biological males seeking female reassignment consists primarily of estrogen administered either orally or transdermally. Prior to initiating estrogen therapy in these patients, serum levels of free testosterone, fasting glucose, liver function tests, complete blood count, and prolactin levels should be drawn. Laboratory evaluation should be repeated at appropriate intervals, generally annually after the first year of estrogen therapy. Consideration of patient age, cardiovascular health, cigarette smoking, obesity, and other comorbidities should be given when prescribing estrogen to male-to-female transsexuals. Side effects of estrogen therapy in these patients include increased risk of venous thromboembolic events, benign pituitary prolactinomas, infertility, weight gain, emotional lability, liver disease, gallstone formation, somnolence, hypertension,

and diabetes mellitus. Typical effects of estrogen therapy in this patient population include breast growth, redistribution of body fat in a female distribution, decreased upper body strength, softening of skin, decrease in body hair, slowing or stopping of loss of scalp hair, decreased fertility and testicular size, and less frequent and firm erections. Males receiving estrogen therapy should be monitored for breast cancer. These patients should continue to be monitored for pelvic malignancies such as prostate and testicular cancer.[123]

Medical therapy for biological females seeking male reassignment primarily involves testosterone administration. Prior to initiating testosterone therapy, liver function tests and a complete blood count should be drawn. These tests should be repeated annually after the first year of therapy. The same considerations that are given to male-to-female transsexual patients should be given to female-to-male transsexual patients prior to prescribing hormone therapy. Side effects of testosterone therapy in female-to-male transsexuals include infertility, acne, emotional lability, increase in sexual desire, increased risk of cardiovascular disease secondary to shift in lipid profile, increased risk of benign and malignant liver tumors, and hepatic dysfunction. Typical effects of testosterone therapy in this patient population include deepening of the voice, clitoral enlargement, mild breast atrophy, increased facial and body hair, male pattern baldness, increased upper body strength, weight gain, and increased sexual interest and arousability. Females receiving testosterone therapy who have not undergone mastectomy and those who have a family history of breast cancer should continue to be monitored for breast cancer. These patients should continue to be monitored for pelvic malignancies.[123]

CLINICAL NOTES

- Lesbian and bisexual women are part of our patient population. Their sexual identities may change over time, so it is important to discuss sexual history and behavior at each visit.
- Lesbian and bisexual women are at risk for the same kinds of health problems as other women. However, they may have an increase, a decrease, or negligible difference in disease risk based on demographic and behavioral factors.
- Lesbian and bisexual women encounter many barriers to health care, including, but not limited to, difficulties in finding a lesbian-friendly health care provider, concerns for discriminatory treatment, concern for compromised confidentiality, lack of cultural competency, lack of a perceived need for routine gynecologic care, and a variety of financial barriers.
- Lesbian and bisexual women are at risk for STIs. HPV, HSV, HIV, gonorrhea, chlamydia, trichomoniasis, syphilis, and hepatitis A and B have all been reported in lesbian and bisexual women. Women with bisexual behavior are more likely to contract an STI than a woman with exclusive lesbian sexual activity.
- BV is commonly found among women who have sex with women and frequently occurs in both members of monogamous lesbian couples.
- Safer sex measures include using barrier protection (condoms on a penetrative sex toy, dental dams for oral–vaginal and oral–anal sex) and proper cleansing of sex toys. For women who also have sex with men, condoms should be used during vaginal or anal sex; condoms should also be used if there is oral-penile contact.
- There are large population-based studies that demonstrate that lesbian and bisexual women are more likely to have a higher BMI and be obese, use alcohol, and use tobacco. Lesbian women are also less likely to have used oral contraceptives or have ever been pregnant.
- Lesbian and bisexual women have a greater incidence of depression, anxiety, posttraumatic stress, and suicidal thoughts than heterosexual women.
- Intimate partner violence may occur in same-sex relationships.
- Lesbian and bisexual adolescents need anticipatory guidance, accurate and nonjudgmental information, and appropriate counseling. They are at increased risk of having unprotected sex; becoming pregnant; using alcohol, tobacco, and recreational drugs; becoming homeless; becoming victims of and perpetrating violence; and attempting suicide.
- Lesbians may choose to be parents in a variety of ways. Children in lesbian households show no significant differences in toy, game, activity, dress, or friendship preferences compared to heterosexual households. Studies of adolescent children from same-sex families show no significant differences in psychosocial adjustment, school outcomes, and romantic relationships.
- Aging lesbians face challenges when seeking needed medical and supportive services. They often do not have family to help with long-term care but have to rely on friends and community members. Committed same-sex couples are denied recognition; they are denied substantial spousal and survivor benefits that are inherent for heterosexual married couples.

(continues)

- Civil unions and domestic partnerships do not provide the same rights as civil marriage. They are not recognized in most other states and are not recognized by the federal government.
- Civil marriage grants legal recognition to the relationship between two individuals. It provides protection for individuals and families, including the ability to be involved in treatment decisions, hospital visitation, the ability to make decisions for the medical treatment of children, better access to health insurance, tax benefits, Social Security benefits, and inheritance rights.
- Essential life planning documents are important for all individuals but especially for same-sex couples. These include a last will and testament, durable power of attorney, a living will or advanced directive, a health care proxy or medical power of attorney, and nomination of guardian for a minor or (ideally) second parent adoption.
- Transgendered individuals believe that they were born into a body with the wrong physical gender. It is not an issue of choice. It is not an indication of their sexual orientation.
- Transgendered individuals may present to the office for routine health maintenance and preventive care. The gynecologist can assist with treatment and/or refer to the appropriate consultants and provide resources for education and support.

WEBSITE RESOURCES

Cancer
The Mautner Project for Lesbian Health. **www.mautnerproject.org**
Cultural competency
"Removing the Barriers" **www.mautnerproject.org**
General lesbian health
National Library of Medicine. **www.nlm.nih.gov/medlineplus/gaylesbianhealth.html**
UCSF, Lesbian Health Research Center. **www.lesbianhealthinfo.org**
Information for parents of gay and lesbian children
Parents, Families, and Friends of Lesbians and Gays. **www.pflag.org**
Medicolegal information
Human Rights Campaign. **www.hrc.org**
Lambda Legal Defense and Education Fund. **www.lambdalegal.org**
National Center for Lesbian Rights. **www.nclrights.org**
Provider support, education, advocacy
Gay and Lesbian Medical Association. **www.glma.org**
Seniors/aging
Services and Advocacy for Gay, Lesbian, Bisexual and Transgender Elders. **www.sageusa.org**
Sexually transmitted infections
Lesbian and Bisexual Women's Health University of Washington at Seattle. **www.lesbianstd.com**
Transgender
World Professional Association for Transgender Health. **www.wpath.org**
Youth
Advocates for Youth. **www.advocatesforyouth.org**
Children of Lesbians and Gays Everywhere. **www.colage.org**
Gay, Lesbian and Straight Education Network. **www.glsen.org**
National Coalition for Gay, Lesbian, and Bisexual Youth. **www.outproud.org**

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CHAPTER 26

Office Evaluation of Women With Disabilities

Caroline Signore

Disability, by any of a number of definitions, will affect most people, either temporarily or permanently, over the life course. Prevailing definitions of disability are of two general forms: medical and social. In the first sense, exemplified by language in the Americans with Disabilities Act,[1] disability is defined as "a physical or mental impairment that substantially limits one or more major life activities." In this paradigm, disability is centered in the individual, as a result of a disease or injury, for example. On the other hand, the social model of disability, preferred by many persons with disabilities and their advocates, views disability as centered in an unaccommodating social or built environment. Members of the disability community resist being defined by their impairments, and instead often view disability as a condition imposed upon them by restrictions in society.

Similarly, the definition of health among persons with disabilities may take different forms based on individual perspectives. For many, the presence of a disabling condition in an individual defines them as "unhealthy." This mental framework may contribute to the misconception that health promotion and preventive care are unnecessary or futile in people with disabilities. However, while people with disabilities are more likely than nondisabled individuals to consider themselves in fair to poor health, 74% of people with nonsevere disabilities and 36% of people with severe disabilities consider themselves to be in good to excellent health.[2] Clinicians providing care to people with disabilities should understand that improving and maintaining health and well-being is as much a priority for them as it is for others.

Thus, people with disabilities require and deserve the same access to disease screening, preventive services, and treatment as the nondisabled. It is well known, however, that individuals with disabilities face significant barriers to care and frequently report unmet health care needs.[3] These barriers include difficulty finding a physician accepting publicly funded health insurance, lack of access to transportation, architectural barriers in and around buildings and offices, and perceived limitations in health care providers' knowledge and understanding of a disabling condition (Fig. 26.1).

Women with disabilities specifically report difficulty accessing high-quality reproductive health care. In one survey of women with physical disabilities, 33% reported they could not access the gynecologic care and counseling they needed.[4] Women with disabilities are less likely than the general population to receive cervical and breast cancer screening. In one study, women with severe functional limitations were 57% less likely to receive regular Pap smears than women without disabilities.[5]

This underserved population thus faces substantial physical and attitudinal barriers to gynecologic care. This chapter aims to describe the population of women with disabilities and to provide guidance for clinicians on conducting a thorough and sensitive outpatient gynecologic evaluation in women with a variety of disabling conditions.

EPIDEMIOLOGY

Prevalence and Scope of Disability Among Women

According to 2006 U.S. Census data, more than 21 million American women and girls aged 5 years and older report a disability[6] (see Table 26.1). The prevalence of disability increases with age, and the total number of women with disabilities is expected to increase with the aging of the baby boom generation. Disability is frequently viewed as occurring in one of three domains: physical, sensory or communication, and intellectual (also known as developmental, mental, or cognitive). The three most common causes of disability in women are arthritis or rheumatism, back or spine problems, and heart trouble.[7] Rates of disability are highest among non-Hispanic blacks, and lowest among Asian/Pacific Islanders (Fig. 26.2). Additionally, the prevalence of severe disability is highest among non-Hispanic black women.

Demographic Characteristics

Compared to nondisabled women, women with disabilities have lower levels of educational attainment, lower rates of employment, lower wages when employed, and higher likelihood of living in poverty.[8] They are more

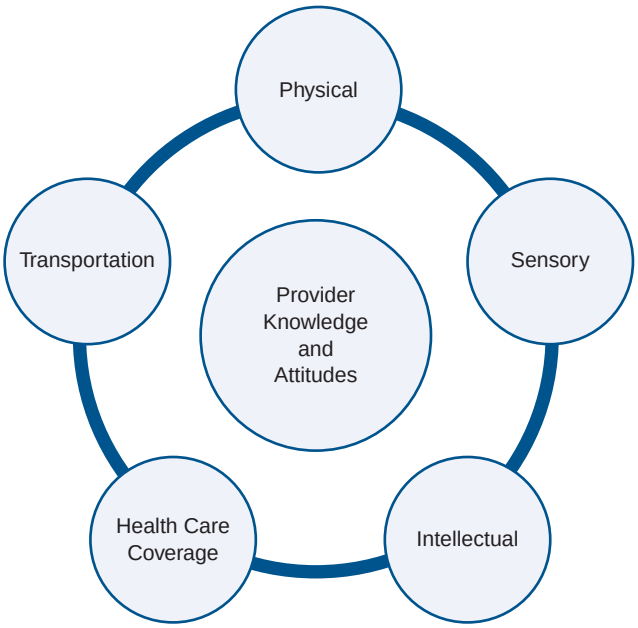

FIGURE 26.1 Barriers to care. (Adapted from American College of Obstetricians and Gynecologists. Reproductive health care for women with disabilities. Interactive site for clinicians serving women with disabilities. http://www.acog.org/departments/dept_notice.cfm?recno=38&bulletin=4526. Accessed December 5, 2013.)

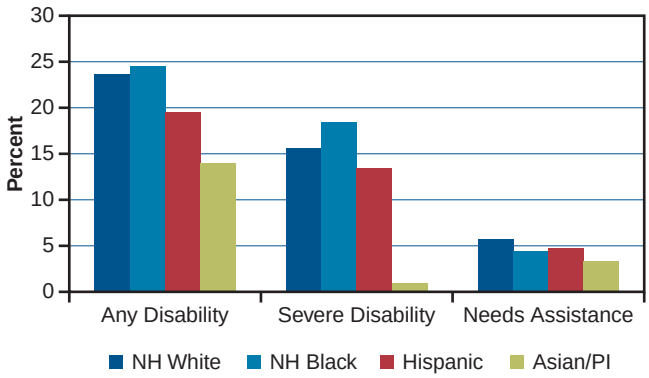

FIGURE 26.2 Disability prevalence among women age 15 years and older, by severity and race/ethnicity, 2002. Disability was defined as difficulty performing functional activities (e.g., seeing, walking), difficulty with activities of daily living (e.g., bathing, eating), difficulty with instrumental activities of daily living (e.g., managing money and bills, going outside the home), or presence of a learning disability or other mental or emotional condition. Severe disability was defined as use of a mobility aid; inability or need for assistance to perform one or more functional activities, activities of daily living, or instrumental activities of daily living; mental retardation, another developmental disability, or Alzheimer disease; a mental or emotional condition that seriously interfered with everyday activities; or limitation in the ability to work around the house or remain employed. (Data from U.S. Census Bureau. *Survey of Income and Program Participation*. Washington, DC: U.S. Census Bureau; 2002.[2])

likely to have publicly funded health care coverage but are at high risk of being underinsured.[9] Women with disabilities are less likely to be married and are at higher risk for social isolation. Trouble accessing transportation is a major problem for many people with disabilities and can lead to geographic isolation. Many women with disabilities are unable to drive or cannot afford an accessible vehicle for personal use. Public transportation may be unavailable or difficult to access. Paratransit services, when available, are frequently unreliable.[10]

TABLE 26.1 Selected Disability Measures, Noninstitutionalized Females Ages 5 Years and Older, United States, 2006

Population	Number	Percentage
All females ages ≥5 y	140,301,572	100
With any disability[a]	21,897,563	15.6
With a physical disability[b]	14,798,702	10.5
With a mental disability[c]	8,031,256	5.7
With a sensory disability[d]	5,753,176	4.1
With a self-care disability[e]	3,426,319	2.4
With one type of disability	9,299,399	6.6
With two or more types of disabilities	12,598,164	9.0

[a]The Census Bureau defines disability as a "long-lasting sensory, physical, mental, or emotional condition or other conditions that make it difficult for a person to do functional or participatory activities such as seeing, hearing, walking, climbing stairs, learning, remembering, concentrating, dressing, bathing, going outside the home, or working at a job."
[b]Defined as "yes" response to presence of a long-lasting "condition that substantially limits one or more basic physical activities such as walking, climbing stairs, reaching, lifting, or carrying."
[c]Defined as "yes" response to the presence of a "physical, mental, or emotional condition lasting 6 months or more" that makes "learning, remembering, or concentrating" difficult.
[d]Defined as "yes" response to presence of long-lasting "blindness, deafness, or a severe vision or hearing impairment."
[e]Defined as "yes" response to the presence of a "physical, mental, or emotional condition lasting 6 months or more" that makes "dressing, bathing, or getting around inside the home" difficult.
From U.S. Census Bureau. 2006 American community survey. http://www.census.gov/hhes/www/disability/2006acs.html. Accessed December 5, 2013.

THE OFFICE ENCOUNTER

Americans With Disabilities Act Requirements and Incentives

Passed in 1990, the Americans with Disabilities Act (ADA) is the landmark civil rights legislation intended to eliminate discrimination against individuals with disabilities. Its four titles apply to employers, public and private entities and telecommunication services, and require these covered entities to provide equivalent access to programs and services to people with disabilities. Health care providers are most impacted by Title III of the ADA, which mandates certain accommodations in private entities. Title III requires places of public accommodation, including professional offices of health care providers, to reduce environmental barriers by modifying physical access if such modifications are readily achievable. The ADA spells out particular architectural accessibility requirements for buildings constructed after 1992 (http://www.ada.gov/stdspdf.htm). Older buildings may be required to renovate or retrofit in order to be in compliance, if such renovations can be reasonably accomplished. Any facility that is undergoing extensive remodeling is required to include accessibility features as specified in the Act and its

regulations. Owners of buildings in which offices are leased may be responsible for access improvements under the law in some cases. Whether removal of a physical barrier is readily achievable or not is judged on a case-by-case basis, taking into account the cost of the modification and the financial resources of the covered entity, among other things. Tax credits and incentives are available for businesses that incur expenses for removal of barriers or improving access to persons with disabilities (see http://www.ada.gov/archive/taxpack.htm for details).

The ADA requires accommodations beyond physical space alterations, for example, by prohibiting discrimination against persons with disabilities in the form of restrictive actions or policies. Under the ADA, exclusion, segregation, or unequal treatment of individuals with disabilities is not permitted. Thus, denial of service to a woman because of her disability is prohibited. Similarly, women with disabilities cannot be denied equal opportunity to access services, for example, by a policy requiring a driver's license for identification. Individuals with disabilities cannot be required to receive services in a segregated location (e.g., entry through a back door or waiting in a separate waiting room), unless such a location or arrangement is the only accessible means for her to receive services.

Covered entities are also required by the ADA to provide auxiliary aids and services necessary to ensure equal access to services to individuals with disabilities that substantially limit the ability to communicate, such as vision, hearing, or speech impairments. Auxiliary aids and services sufficient to ensure effective communication are required at the covered entity's expense; the type of aid or service required depends on the length and complexity of the communication involved. A common situation to which this provision applies is the requirement for covered entities to provide a qualified sign language interpreter for an individual with a hearing impairment who communicates using sign language and must discuss complex medical information with a health care provider. Other examples include Braille and large-print reading materials, or reading a patient information pamphlet, consent form, or bill aloud to a woman with low vision. Providers are encouraged to consult directly with women with disabilities to determine what type of aid or service will ensure effective communication.

The nondiscrimination requirements of the ADA are not limitless. Entities may raise a number of key defenses to a charge of discrimination under the ADA. Failure to provide an accommodation may be defensible if (a) provision of the accommodation would fundamentally alter the nature of services provided by the entity; (b) providing the accommodation would cause the entity undue burden, defined as "significant difficulty or expense"; or (c) providing the accommodation would cause a direct threat to others. In each case, the entity accused of discrimination bears the burden of showing that failure to provide the accommodation meets the defense standard; this is judged on a case-by-case basis. Details on the requirements and limitations of ADA Title III are discussed in the ADA Title III Technical Assistance Manual (http://www.ada.gov/taman3.html).

Physical Access

Office practices must ensure adequate physical access for women with disabilities, from parking, to building and office entryways, to waiting areas, reception counters, restrooms, hallways, and examination rooms.[10] Growing attention is being given to the concept of universal design in the built environment, in which facilities are designed to be inherently accessible and usable by the maximum number of individuals, regardless of ability.[11]

Improving access in the office will serve not only to make a woman's visit more comfortable, it will allow the provision of better care. In some cases, substantial structural remodeling may be needed, but other simple steps and modifications to office procedures can simplify a woman's visit. Offices can improve access for women with disabilities by the following:

- Ensuring that there is at least one reserved accessible parking space and that there is a safe and barrier-free (i.e., no curbs or steps) path between the parking space and entrance.
- Installing ramps to overcome architectural barriers. Ramps may be purchased or built and must include 12 inches of length for every 1-inches increase in elevation.
- Enlarging door widths to at least 30 inches; 32- to 36-inches doorways are ideal.
- Removing or adapting doorway thresholds that are not flush with the floor.
- Ensuring that trash cans, plants, or other items do not block elevator call buttons.
- Locating a building directory so it is visible from wheelchair height; using a font large enough to be read by people with vision impairment.
- Installing a power door opener or a doorbell for use by people who cannot open a door independently.
- Exchanging round doorknobs with "lever" door handles.
- Having at least a portion of the reception desk lowered to wheelchair height.
- Mailing long medical history and other intake forms to patients in advance.
- Training reception staff to come around the desk to assist patients with check in, especially if the reception desk is not lowered. Offering assistance with completing forms in a private location.
- Preserving a space for a wheelchair in the waiting area.
- Clearing boxes, equipment, or other items from office hallways.
- Allowing flexibility in scheduling to accommodate late arrivals related to transportation difficulties. Scheduling longer appointments to accommodate patients' additional needs (e.g., assistance with forms,

undressing or transfer assistance, communication through an interpreter).
- Inviting women with disabilities to assess office layout and practices and make suggestions for improvement.

Communication

Providing quality primary and preventive care relies heavily on communication; this is especially so for care visits for women with disabilities. Practitioners and staff should avail themselves of the expertise each woman with a disability holds about her condition, her specific needs, and how those needs can be addressed. Asking a woman questions about her disability and how she believes it may relate to any health concerns is not only greatly informative, but it demonstrates respect and that her input is valued.[10]

Barriers to effective communication need to be addressed. Women with hearing impairments may choose to communicate in one or more of a number of ways, including American Sign Language, other manual signs, speech-reading (or lip reading), or cued speech (a combination of speech reading and hand cues). Clinicians should ask women who are deaf or hard of hearing how they would prefer to communicate and then comply with that preference[12] with flexibility and adapting to the needs of the situation.[8]

Assistance and Accommodation

One of the first accommodations a woman with a disability may require for a quality gynecologic office visit is time. Additional assistance and support in the office and examination room are frequently needed, ranging from help completing paper-based history and insurance forms, assistance with undressing, transfer to the examination table, completion of a pelvic examination, or discussing a management plan through a sign language interpreter. Scheduling staff can facilitate quality care by asking new patients if they will need any special assistance during their office visit, and adjusting appointment length accordingly.

Plan to perform the patient's history and physical examination in the largest, most accessible room or rooms possible, keeping in mind the width of hallways and doors. Practicing the steps needed to provide a competent and successful office encounter can ensure that when women with disabilities present for care, their experience is as comfortable as possible.

HISTORY

In many cases, a woman's disabling condition and reproductive health will have important and unique reciprocal influences on each other. It is important to remember, though, that women with disabilities may experience any health or wellness concern that nondisabled women experience, and no assumptions should be made that any part of a standard gynecologic care visit is irrelevant because of a woman's disability. As with all women, the content of a primary care encounter should include age-specific routine assessment, health status assessment (nutrition and exercise), routine screening for and prevention of disease, assessment and management of psychosocial issues, and family planning.[13] The following are key topics that should be routinely addressed when taking a medical history from a woman with a disability.

Menstrual History

Normal menstruation may pose unique challenges for women with disabilities. Maintaining menstrual hygiene can be difficult for women with limited mobility and uterine cramping may trigger increased spasticity and other neurologic symptoms. Women with intellectual disabilities can experience behavior problems associated with menses. Approximately 50% of women with epilepsy report increased seizure activity around phases of the menstrual cycle.[14] The difficulties faced by women with disabilities may be compounded when there are menstrual abnormalities such as irregular or heavy bleeding and significant dysmenorrhea. Ask women how their menses affect their daily lives and if they have any concerns. Interviewing caregivers or attendants who assist with menstrual management may be necessary; menstrual calendars can facilitate collection of this history.

Sexuality

Taking an adequate sexual history is a commonly omitted component of routine gynecologic health care, and this may be especially so for women with disabilities. There is a tendency to view a woman with a disability as genderless, asexual, or uninterested in sex; however, at least 70% of women with physical disabilities are sexually active[15] and the majority want information on sexuality.[16] A disabling condition may interfere with sexual function by limiting movement, making movement painful, or altering the physiology of the sexual response. Other factors affecting sexuality in women with disabilities include fatigue, concerns about safety, medication use, self-esteem and body image, and mental health and stress. Clinicians will likely need to lead discussions on sexuality and should approach the topic directly and nonjudgmentally, letting women know that sexuality is a part of health and that there are strategies for addressing sexual dysfunction.

Just like other women, women with disabilities are at risk for sexually transmitted infections (STIs) and should be screened appropriately. This is especially important for women with intellectual and developmental disabilities (IDD), who may find it difficult to give an accurate sexual history. In addition, women with decreased upper extremity mobility and dexterity may find barrier

methods of contraception difficult to use.[9] In women with disabilities, symptoms of STIs may be unperceived or may be ascribed to a urinary tract infection without investigation, thus diagnosis is often delayed.[17]

Pregnancy Planning and Contraception

Fertility is not impaired in most women with disabilities and a woman's desires and plans for pregnancy or contraception should always be discussed. Each encounter with a woman of reproductive age is an opportunity to review her family planning needs, provide preconception counseling, or assess her satisfaction with current birth control methods. Many women with disabilities report, however, that they are hesitant to ask questions, and that contraceptive information is not offered to them.[16]

There are scant data to guide the choice of contraceptive method for women with disabilities. When making recommendations, clinicians should consider whether the patient will be capable of administering the method herself or require assistance, what her needs for STI prevention are, what the effects on menses and menstrual hygiene may be, and how the contraceptive method may interact with the disabling condition (e.g., potential increase in thromboembolism risk with combination oral contraceptives in women with mobility impairments). For women with developmental disabilities, it is important to probe the motivation for caretaker requests for contraception and assess the possibility of coercive sexual activity.

Women with disabilities frequently report feeling pressure not to conceive, for both medical and social reasons. In reality, existing data indicate that the majority of pregnancy outcomes among women with disabilities are good. With the right services and supports, many women with disabilities are fully capable of being loving, supportive parents. Preconception planning is recommended[18] and should address genetic counseling; interactions between pregnancy and the disabling condition; any needed adjustment of medications; and developing plans for labor, delivery, and the transition to parenthood.

Substance Use

Illicit drug use is more common among women with disabilities than in the general population, with risk factors including chronic pain, use of prescription drugs, social adjustment difficulties, having friends who use drugs, and being a victim of substance abuse–related violence.[19] In some cases, substance abuse is overlooked or viewed by other individuals as an "entitlement" a person with a disability deserves as compensation for bearing the burden of his or her impairments.[20]

Most reports suggest that women with disabilities consume alcohol at rates and amounts similar to those of women in general, but some evidence suggests that women with disabilities may use alcohol in excess[21] or more often than their nondisabled counterparts. Smoking is more common among people with disabilities than the general public. Beyond the well-known adverse health effects of smoking, for women with physical disabilities and mobility impairment, tobacco use increases the risk of decubitus ulcer formation and impairs wound healing.

Thus, assessment of drug, alcohol, and tobacco use is an important component of care, and when substance use or misuse is suspected, women should be referred for evaluation and treatment.

Mental Health

Women with disabilities are more likely to report depression, anxiety, and stress than the general population.[22–24] In general, the prevalence of depressive symptoms increases with severity of disability and functional impairment and is also associated with adult onset of disability, chronic pain, and poor satisfaction with personal support. Despite higher prevalence of depressive symptoms, women with disabilities are less likely to receive treatment for depression.[25] Clinicians should remember that depression and other mental health disorders are not integral parts of disability and, when present, these conditions should be treated.

Abuse

Clinicians should screen all women for domestic and intimate partner abuse. Although the lifetime occurrence of emotional, physical, or sexual abuse is similar for women with and without physical disabilities,[26] women and girls with IDD are at increased risk for sexual assault and abuse.[27] Women with disabilities are vulnerable because it may be difficult for them to flee an abusive situation, and they experience longer duration of abuse[26] than women without disabilities. A troubling aspect is that women with disabilities who are abused are frequently reliant on the perpetrator of the abuse for basic care. Abuse may be disability-related, consisting of denial of disability or withholding of needed equipment, medication, or assistance. Every effort should be made to screen for abuse privately, out of the presence of caregivers. The Abuse Assessment Screen—Disability is a useful tool for detecting abuse of women with physical disabilities[28] (see Box 26.1). Women with IDD may have difficulty recognizing and describing abusive behavior, and clinicians should be vigilant for behavioral or physical signs of sexual abuse.

PHYSICAL EXAMINATION

Equipment, Transfers, and Positioning

One of the first challenges of the physical examination for the patient and her provider may be an accurate measurement of weight. Women who use wheelchairs

BOX 26.1

The Abuse Assessment Screen-Disability (AAS-D)

1. Within the last year, have you been hit, slapped, kicked, pushed, shoved or otherwise physically hurt by someone?
2. Within the last year, has anyone forced you to have sexual activities?
3. Within the last year, has anyone prevented you from using a wheelchair, cane, respirator or other assistive devices?
4. Within the last year, has anyone you depended on refused to help you with an important personal need, such as taking your medicine, getting to the bathroom, getting out of bed, bathing, getting dressed, or getting food or drink?

From McFarlane J, Hughes RB, Nosek MA, et al. Abuse assessment screen-disability (AAS-D): measuring frequency, type, and perpetrator of abuse toward women with physical disabilities. *J Womens Health Gend Based Med*. 2001;10(9):861–866.

and are unable to stand will often be unaware of their actual weight because so few health care facilities have platform scales on which they can be weighed while seated in their wheelchairs. For a relatively small investment, a platform scale will enable all patients' weights to be measured. Calculation of body mass index (BMI) is recommended for all women. Women with physical and intellectual disabilities are at increased risk for overweight and obesity compared to the general population.

Women with physical disabilities identify difficulty getting onto the exam table as the most prominent barrier to gynecologic care.[15] Provided that the examination table height can lower to the level of a wheelchair seat, many women who use wheelchairs will be capable of transferring themselves to the table independently. Offices should aim to have at least one exam table that lowers to 17 to 20 inches in height for this purpose. If such a table is unavailable, or if a woman is unable to position herself for examination independently for any reason, the ADA requires that office staff provide adequate assistance with transfers to the exam table and positioning, including lifting if necessary. Patients themselves will be the best source for guidance on the most appropriate methods of assistance, and they should always be asked their preferred approach to transfers. Staff should be instructed on safe lifting techniques that are adaptable to different women's needs and preferences. Offices can invest in transfer boards (a solid plank used to create a bridge between the seat surface of a wheelchair and the exam table surface) and patient lifts to facilitate safe transition from a wheelchair to the exam table.

Women with disabilities may have impairments in strength, balance, or stability, and may require extra supports or protection while on the exam table. Tables equipped with guardrails are helpful in many cases. To avoid skin injury from friction or shear, use a drawsheet to position patients and avoid prolonged supine positioning that increases risk of injury to skin overlying the sacrum. Make liberal use of padding or bolsters to enhance the patient's safety and stability.

Adaptations to the standard lithotomy position may be necessary. Some women may have pain, joint contracture, or spasticity that limits their ability to comfortably use standard exam table stirrups. Obstetric stirrups that provide under-knee support or full leg stirrups can be very helpful for women who have diminished muscular control of their lower extremities. In some cases, stirrups can be removed and the patient positioned with her feet and limbs on the table surface (Fig. 26.3A–E).[29] Assistants may be needed to position the legs and provide mechanical support during the examination. All positioning movements should be slow and gentle to minimize pain and to prevent injury or exacerbation of any spasticity.

It is impossible to conduct a thorough pelvic exam on a woman while she is seated in a wheelchair; this should not be attempted. Again, women with disabilities are the best source for information about what they see as the best approach to pelvic examination and the amount and type of assistance they need. A good practice is to ask before acting; give patients time to describe exactly what accommodation would be helpful before implementing preconceived ideas. Following any office visit, ask patients how the experience could have been improved and review and refine office accommodations and procedures with staff.

Special Considerations

Women With Physical Disabilities

Spasticity

Spasticity is a frequent secondary condition in individuals with upper motor neuron disorders such as cerebral palsy, multiple sclerosis, or spinal cord injury (SCI). Common components of spasticity include increased muscle tone, tendon jerks, and clonus, which may occur spontaneously or in reaction to stretch or other noxious stimuli.[30] In some cases, long-standing spasticity results in joint stiffness or contractures. Positioning for a pelvic exam may elicit a spasticity reaction that makes maintaining a position difficult. To minimize the effects of spasticity, it is helpful to keep all body movements and positioning maneuvers slow and gentle.

Autonomic Dysreflexia

Autonomic dysreflexia (AD) is a potentially serious complication of high thoracic and cervical spinal cord injuries (T6 and above),[31] although it has been observed rarely with injuries at lower levels[32] and in other conditions such as multiple sclerosis.[33] The clinical syndrome, characterized by severe hypertension, results when a noxious stimulus below the level of the spinal cord lesion elicits a reflexive sympathetic discharge, which

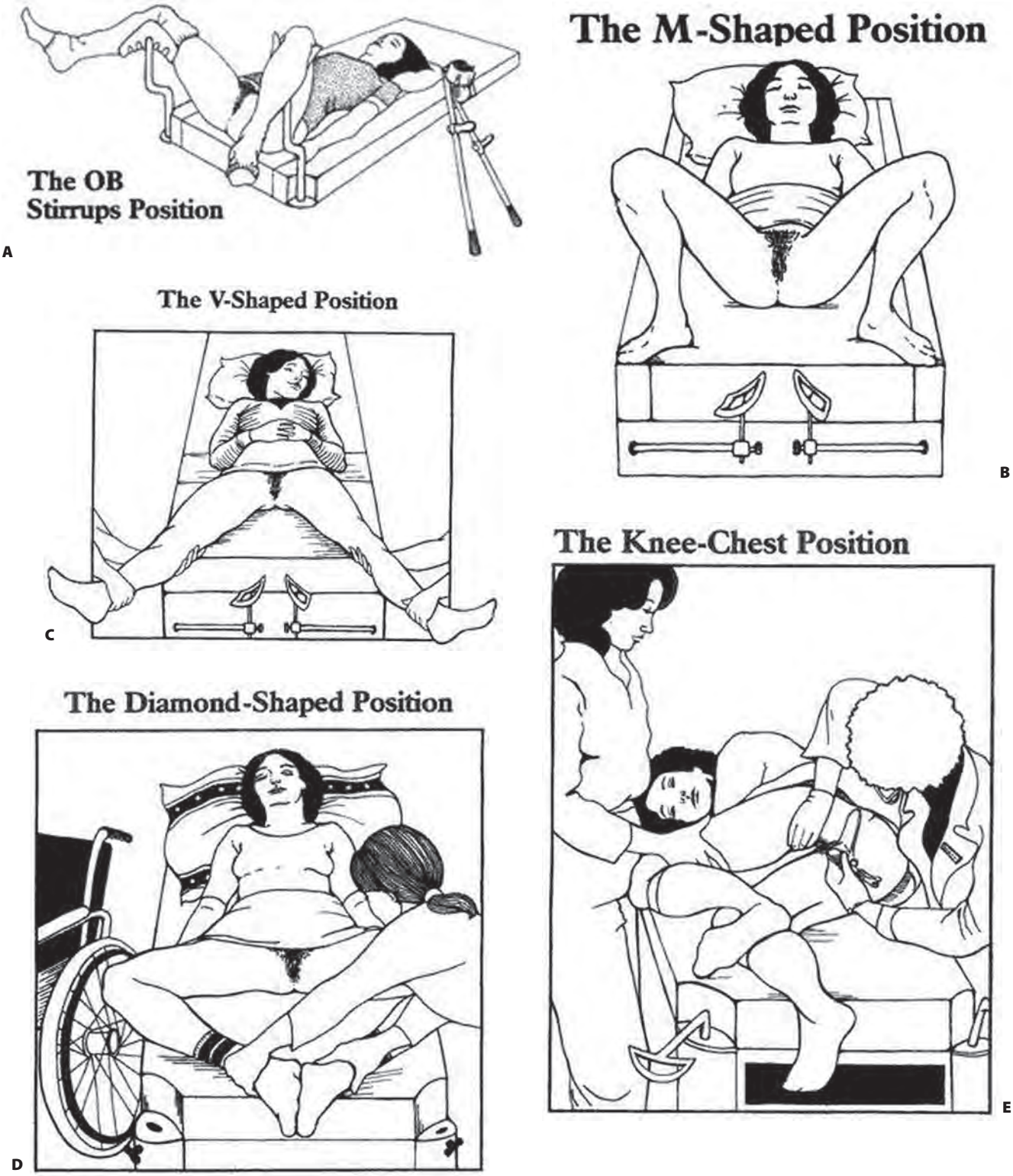

FIGURE 26.3 Alternative positions for gynecologic examination. **A:** The OB stirrups position. **B:** The M-shaped position. **C:** The V-shaped position. **D:** The diamond-shaped position. **E:** The knee–chest position. (From Simpson KM. Table manners and beyond: the gynecological exam for women with developmental disabilities and other functional limitations. http://www.bhawd.org/sitefiles/TblMrs/cover.html. Accessed October 18, 2010, with permission.)

cannot be moderated by the normal brainstem response mechanisms.[34] The most common precipitating stimuli are distension or irritation of the bladder or bowel, such as with an overdistended bladder, cystitis, urinary instrumentation, or fecal impaction. Other important causes in women include labor, menstruation, sexual activity, and pelvic examination. The hypertension associated with AD may be marked, with systolic pressure reaching 300 and diastolic, exceeding 200 mm Hg; however, because baseline blood pressure is chronically low in SCI,[35] even an apparently "normal" blood pressure may be a substantial elevation for a woman with SCI. Other signs and symptoms of AD include bradycardia, electrocardiographic changes, pounding headache, piloerection, flushing, diaphoresis, and anxiety and apprehension. In extreme cases, AD can result in intracranial hemorrhage, seizures, coma, and death.

Clinicians may hesitate to recommend and perform pelvic examinations in women with SCI for fear of inducing AD, thus women may not have been examined regularly or at all in the past. Women with SCI can report their history of AD and its severity and can provide insight into its prevention during an examination. The key to management of AD is recognizing precipitants and making efforts at prevention during an examination. For all exams, the bladder should be empty and gentle technique employed. If AD does occur during a pelvic examination, the first response should be to cease the exam immediately. Patients should be assisted into an upright, seated position to promote an orthostatic decrease in blood pressure. Blood pressure should be monitored frequently and usually responds well to these measures. If there is no response, another precipitating source for AD, for example bladder distension, should be sought and addressed. Persistent hypertension may be treated with a rapid-onset, short-acting antihypertensive such as nifedipine or nitrate paste.[34]

Skin Inspection

Decubitus ulcers are a common cause of morbidity in women with physical disabilities. Early recognition and treatment of skin injuries are key strategies to preventing development of advanced wounds and their complications. Two-thirds of pressure ulcers occur around the pelvis.[36] Thus, the gynecologic examination is a unique opportunity to carefully assess skin areas at high risk of injury, that is, regions overlying the ischial tuberosities and greater trochanters. Risk factors for decubitus ulceration include limited mobility, sensory impairment, incontinence, smoking, poor nutrition, and extremes of weight. Clinicians should familiarize themselves with the appearance and management of pressure ulcers and make appropriate referrals for evaluation and care if skin injury is detected on exam.

Latex Allergy

Allergy to latex is present in 1 to 2% of the general population, but 20 to 67% of individuals with spina bifida have immediate sensitivity reactions to latex.[37,38] This is believed to be due to multiple early life exposures of mucous membranes to latex experienced by those born with neural tube defects. Prevalence of latex allergy increases with the number of prior surgeries.[37]

Cervical Cancer Screening and Breast Health

Studies have shown that women with functional limitations have lower rates of cervical cytology screening than women without disabilities, with barriers including physical difficulty with transfers and positioning for the exam, trouble finding a willing practitioner, or perceptions by clinicians that women with disabilities are not susceptible to human papillomavirus (HPV) infection and that screening is therefore unwarranted.[8,15] Recommended guidelines for cervical cancer screening apply to all women, including those with disabilities. Reasonable modifications to the recommended screening frequency can be made in consultation with the patient based on her ability to tolerate the examination and assessment of risk factors for HPV infection.[8]

Breast cancer screening guidelines are also no different for women with disabilities, yet women with functional limitations are less likely to receive mammography screening than women without limitations.[39,40] Again, difficulty getting into or maintaining the position for mammography is identified as the primary barrier to accessing this service.[4] Many machines are not built to accommodate women who are seated in a wheelchair. Women with trunk instability or movement disorders may require assistants to help them lean forward or be still for the image. Staff or companions may hesitate to provide needed assistance due to concerns about radiation exposure. Clinicians should make themselves aware of the nearest location of fully accessible mammography equipment.

Women with impaired upper extremity mobility or sensation and women with visual impairment may not be able to perform self-breast inspections and examinations themselves. Although the United States Preventive Services Task Force has recently recommended against clinicians instructing women on self-breast examination techniques,[41] the American College of Obstetricians and Gynecologists maintains its position that routine self-breast examination may lead to detection of breast cancer and can be performed.[42] Clinicians can instruct trusted caregivers on how to perform or how to assist women with disabilities to perform regular breast examinations.

Women With Intellectual and Developmental Disabilities

The American Association of Intellectual and Developmental Disabilities[43] defines intellectual disability as the development before age 18 years of "significant limitations both in intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills." Some intellectual disabilities may be

acquired in adulthood, for example, from traumatic brain injury.

Communication and Education

Taking steps to optimize communication with a patient with IDD can make the office encounter and exam much more pleasant and productive for all. It is helpful to first see the patient while she is still dressed, in an area with few distractions, adopting an unhurried manner and addressing her directly. To the extent possible, ascertain the reason for the visit and pertinent history from the patient herself, or ask her permission to seek information from family or attendants with her. Obtaining a sexual history is particularly important, both to initiate conversation and education about sexuality, consensual relationships, and sexual health, and also to screen for abuse and teach women how to avoid unwanted and inappropriate sexual activity. Messages should be concrete, developmentally appropriate, and repetitive to enhance understanding.[8]

Resistance to Examination and Issues of Consent

It is not uncommon for women with IDD to be resistant, unpredictable, or hostile when faced with the prospect of a gynecologic exam. Their reactions may be based in fear or mistrust resulting from unwanted contact, sexual abuse, or coercive examinations in the past. Women with IDD may also have physical disabilities that need to be accommodated as well. Before assisting women with positioning and the exam, take care to explain your actions and what will occur. There are insufficient data to support a policy of routine medical sedation of women with IDD in order to perform a pelvic examination. In one study of women with IDD, the adequacy of cytology specimens collected did not differ between women who received oral sedation for the exam and those who did not.[44] Use of a small-bladed, warmed speculum, and/or a single finger vaginally or rectally during bimanual examination may facilitate accomplishing the examination.

For some women, though, speculum and/or bimanual examination during an office encounter will not be possible. Subsequent action depends largely on the indications for the examination. Some patients will be brought to the office with a directive for a Pap smear. However, there is no legal requirement that cervical cytology be included in a reproductive health evaluation. If the woman is asymptomatic and has presented for routine screening and preventive care, an assessment of risk factors for cervical dysplasia should be attempted. Guidelines on cervical cancer screening intervals[45] apply to all women, regardless of disability, but can be reasonably adjusted according to a patient's risk status. In some cases, a blind Pap test, in which a moistened cotton swab is inserted along the examiner's finger to sample the cervical surface without direct visualization, may be attempted.[44] This method yields suboptimal endocervical cell sampling but may be a reasonable option for women unable to tolerate speculum insertion. Another consideration is HPV DNA detection.[46] On the other hand, a woman's history and clinical signs may warrant a complete examination that is only achievable under anesthesia. In these cases, great care should be taken to ensure that the benefits of the exam outweigh the risks of the anesthesia. Coordinating with other providers for delivery of additional needed health services (e.g., dentistry, sigmoidoscopy) while the patient is anesthetized can maximize the value of proceeding with examination under anesthesia.

In some cases, family members, caregivers, or other attendants may bring a patient to the office with a request for contraception, sterilization, or other surgical procedures. These situations can be ethically complex. It is important to ascertain the motivation behind the request, investigate the possibility that coercive sexual activity is occurring, and be cognizant that caregivers' and the patient's interests may not be aligned. To the greatest extent possible, assess what the patient's own views and desires are in regard to her fertility. Consenting women with IDD are entitled to develop relationships, have sexual lives, and consider having children. Patient education and reversible contraception should be considered as first steps to preventing unwanted or poorly timed pregnancy. The presence of an intellectual or developmental disability does not, in itself, justify requests for sterilization or their denial.[47] When surgical sterilization is considered, clinicians bear the responsibility for determining whether the patient is capable of providing informed consent. This can be challenging and requires knowledge of local, state, and federal laws, regulations, and definitions of competence. Consultation with ethical review boards and other individuals with expertise in the field is often warranted. When a woman is not able to provide informed consent, the physician must work with family and other caregivers to develop a plan that is based on the patient's best interests, maximizes her autonomy, and honors her values and beliefs about reproduction to the greatest extent possible.[48]

Women With Sensory Disabilities

Communication

For women who are deaf or hard of hearing, the predominant barriers to care are breakdowns in communication. Difficulty may begin when a patient needs to call the office for an appointment. Providers should be aware of a nationwide free program, Telecommunications Relay Service, which allows the placement or receipt of telephone calls from persons with hearing or speech impairments without the need for special equipment.[49] In the office, individual women should be given the choice of how to communicate during their visits, and they may choose more than one modality. Women with hearing impairments who use sign language are entitled under the ADA to have a qualified medical interpreter provided to them for exchange of medical information. During these encounters, practitioners should take care to maintain eye contact with and address questions and

responses to the patient, not the interpreter. Family members or friends who sign are not qualified medical interpreters and are therefore not appropriate for most clinical situations in women's health care. Beyond compromising patient privacy and open discussion, lay interpreters are likely unfamiliar with signs for medical terms and may cause miscommunication. For the examination, ask the patient where she would like the interpreter to be positioned to balance her needs for privacy and communication. When speaking to a patient who lip reads, it is important to face her directly. Raising the head of the examining table and lowering the drape during a pelvic examination helps ensure a patient can see the examiner when she or he is speaking.

In the exam room, women with visual impairments should be verbally informed about the layout of the room and asked what assistance, if any, she may need. It is often helpful to describe where she can place her clothing, where the exam table is, and how she may approach it. All individuals who enter or leave the room should announce themselves. Similarly, women should be verbally alerted before they are touched. Women who use a cane for mobility may prefer to keep the cane within their reach; staff should not move or relocate the cane without express permission or request from the patient. Certified guide dogs may not usually be excluded from areas where women are seen and examined. It is not appropriate to pet, touch, address, or try to instruct a service animal. They are trained to respond only to their owner's voice and commands and should not be distracted while working.

DISABILITY CULTURAL COMPETENCE

The American population is becoming increasingly diverse, and people with disabilities contribute to this diversity. To minimize disparities in health services and outcomes, providers must develop the insights and skills needed to deliver culturally competent care to members of all minority groups, including people with disabilities. Culture may be defined as patterns of human behavior that include the language, thoughts, communications, actions, customs, beliefs, values, and institutions of racial, ethnic, religious, or social groups that share formative experiences and are influenced by a common history.[8,50] Culturally competent care reflects behaviors, attitudes, and policies on the parts of providers that are respectful of the particular beliefs, needs, and experiences of diverse patients.

Historically, and in the present day, mainstream culture has tended to hold a predominantly negative view of disability, perceiving people with disabilities as sick, burdensome, incompetent, or as objects to be pitied or feared.[51] On the contrary, an emerging disability culture views disability not as a tragic and pitiful circumstance, but rather as a normal part of human variation that virtually all of us will experience to some degree in our lifetimes. By shifting thinking in this new direction, health care providers can eliminate some common barriers and deliver better and more sensitive care.

In health care settings, women with disabilities frequently report that they feel degendered, with their roles as lovers, spouses, and mothers minimized or frankly ignored.[52] Gynecologic care providers have an important role to fill in combating stereotypes and affirming the importance of gender identity and reproductive health in women with disabilities. Asking women about their sexual lives, their needs and desires for contraception, or their plans for pregnancy affirms their social and reproductive roles, respects their dignity, and acknowledges women's legitimate interests in their reproductive health.

No two women with disabilities will have identical health conditions or concerns nor will they necessarily share the same views on what constitutes disability etiquette. However, adopting some fundamental practices, such as using positive language, can improve communication and convey professionalism and respect for women with disabilities. Practical guidelines for enhancing interactions with women with disabilities are listed in Box 26.2. In keeping with the resistance to being defined by impairment, many people prefer "person-first" language, for example "woman with a disability" instead of "disabled woman." Similarly, avoiding the use of negative, tragic language ("confined to a wheelchair," a "victim" of cerebral palsy) is a beneficial step toward acknowledging disability as a mere difference, not a lamentable deficiency.

BOX 26.2

Etiquette for Communicating With People With Disabilities

When speaking with a woman with a disability, look directly at her, not at her companion, assistant, or interpreter.

Offer to shake hands upon introduction.

Always identify yourself and any colleagues when conversing with someone with low vision. Announce when you or others enter or leave the room.

Place yourself in the line of sight to capture the attention of someone who is deaf or hard of hearing. Do not tap someone from behind to announce yourself.

Treat adults as adults.

Be patient and listen attentively to women who have difficulty speaking. Do not try to finish their sentences or thoughts for them. If you have not understood something, do not hesitate to repeat what you have heard and allow the woman to respond.

Do not lean on or use a woman's wheelchair as a prop; it is part of her personal space.

Place yourself at eye level when speaking with someone seated in a wheelchair or on a scooter.

Offer assistance, but wait for the offer to be accepted before acting. Listen for or ask for instructions.

Ask questions. People with disabilities are experts on their own needs and are used to questions.

From Center for Independence of the Disabled in New York, Inc. Sensitivity plus! Etiquette for communicating with people with disabilities. *On Target: Disability and Health in New York State*. vol 9. http://www.health.state.ny.us/nysdoh/prevent/target9.htm. Accessed December 5, 2013.

CLINICAL NOTES

- "Disability" may be defined or viewed in many ways, including from a medicolegal perspective or social perspective. It is important for care providers to be aware of both the medical and social components of disability in women.
- Women with disabilities consistently report difficulty accessing quality reproductive care. Barriers include adverse socioeconomic characteristics, physical accessibility limitations, communication difficulties, lack of access to transportation, and perceived deficiencies in provider knowledge and attitudes.
- Title III of the ADA prohibits private entities, including physician offices, from discriminating against people with disabilities, and requires certain physical space alterations, equalization of access to services, and provision of auxiliary aids and services. Practices can make simple changes that will improve accessibility for women with disabilities.
- Managing menstruation can be difficult for women with disabilities. Ask women if they have menstrual concerns and address them.
- Women with disabilities are often mistakenly viewed as asexual or uninterested in sexuality. Remember to inquire about women's sexual lives and concerns, risks for STIs, needs for contraception, and plans for pregnancy at each visit.
- The evidence base for contraceptive choices for women with disabilities is limited. Prescribing clinicians should consider physical dexterity and ease of use, risk for thromboembolism, need for protection from STIs, potential for troublesome irregular bleeding, and women's long range plans for pregnancy.
- Women with disabilities are at increased risk for substance use, interpersonal abuse, and depression, and should be screened for these conditions and treated or referred as appropriate.
- Approach the physical examination first by asking what assistance the woman may need and follow her guidance to the greatest extent possible.
- Women with physical disabilities may require alternate positioning on the exam table to accommodate joint contractures, spasticity, strength limitations, and needs for bodily support.
- AD is a serious condition associated primarily with spinal cord injuries above the 6th thoracic vertebra, characterized by extreme hypertension, cardiac rhythm disturbances, headache, flushing, piloerection, and other signs and symptoms. The syndrome may be precipitated by pelvic examination and gynecologic procedures and is potentially life-threatening. Treatment consists of ending the examination, removing any noxious stimuli, elevating the head, and use of rapid-acting antihypertensives if necessary.
- Care of women with IDD should be individualized according to a woman's stage of development, ability to communicate, and presenting complaint.
- Ethical issues and obtaining proper informed consent from women with intellectual disabilities can be complex. Clinicians should freely seek input from patients, their families, and experts in relevant fields.
- Establishing and maintaining effective communication with women with sensory or speech impairments is imperative and can be achieved by asking women their preferences, maintaining flexibility, and employing simple interactive techniques.
- Women with disabilities contribute to cultural diversity, and gynecologic clinicians can improve their care delivery and women's well-being by acknowledging the importance of reproductive health, sexuality, and disease prevention among women with disabilities. Using "person-first" and positive language is a way to combat negative stereotypes many women with disabilities confront regularly.

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CHAPTER 27

Management of the HIV-Infected Woman

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Despite the dramatic advances in the treatment of HIV, the epidemic continues to soar, particularly among women. The growing number of women of reproductive age living with HIV is a dominant feature of this disease. HIV-infected women tend to be diagnosed later in the disease process than men and often have poorer access to HIV specialists and medications.[1] They also may have specific vulnerabilities related to poverty, domestic violence, mental health, and responsibilities regarding children, some of whom may also be HIV-infected.[2]

Because most women of reproductive age are healthy, the only time they may visit a physician is for routine gynecologic care. Thus, it is important for the health care provider to be able to recognize the signs and symptoms that might suggest HIV infection so they can be diagnosed early in the disease. This allows for early intervention prior to the onset of opportunistic infections (OIs) with combination antiretroviral therapy (cART) in order to delay the progression to AIDS. In addition, the investigation and management of common gynecologic problems may need to be broadened if the woman is also infected with HIV.

This chapter provides an overview of the diagnosis and primary care of patients with HIV, along with issues unique to HIV-infected women that are related to the transmission of the virus, contraception, reproductive options, and gynecologic manifestations of the disease.

EPIDEMIOLOGY

HIV continues to be a major global health priority, with the proportion of women infected continuing to increase over the past 10 years.[1–5] The World Health Organization (WHO) estimates that at the end of 2011, approximately 34 million people were living with HIV/AIDS, and of these, 16.6 million were women.[1] There is geographic variation in HIV prevalence between and within countries. In 2011, sub-Saharan Africa accounted for 69% of HIV infections worldwide with 23.5 million people living with HIV/AIDS—approximately 60% of whom are women.[1] Women account for 30 to 40% of people living with HIV/AIDS in Asia and Latin America, 30% in Eastern Europe and Central Asia, and 45 to 50% in the Caribbean.[2]

Women have a particular vulnerability to HIV, often compounded by cultural, social, and economic disadvantages.[5] Studies show that women are more likely to acquire HIV from an infected partner during unprotected heterosexual intercourse than men.[6] Gender-based violence and income inequality has also been associated with increased HIV risk.[7–9] Economic disadvantage may increase high-risk behavior among women who may be driven to transactional sex by economic necessity, especially in the setting of migration.[5,7] The rate of HIV infection among female sex workers is high in many parts of the world, many of whom may also use intravenous drugs.[10]

In the United States, the HIV epidemic has recently been described as "low prevalence in the general population, high prevalence among disenfranchised and socially marginalized."[3] It is estimated that there are now greater than 1 million HIV-infected Americans, more than 20% of whom are not aware of their diagnosis.[11] At the end of 2011, 21% of new HIV infections in the United States were in females, predominately through heterosexual contact (86%). In 2011, Black/African American females made up 12% of the female population in the United States but accounted for an estimated 64% of diagnoses of HIV infection among females. Hispanic/Latino females made up 15% of the female population in the United States but accounted for 15% of diagnoses of HIV infection among females. White females made up 66% of the female adult and adolescent population in the United States but accounted for 17% of diagnoses of HIV infection among females.

The rate of new HIV infections among Black women in 2010 was 20 times that of White women and nearly 5 times that of Hispanic women (38.1 versus 1.9 and 8.0 per 100,000, respectively). Hispanic women experienced an HIV infection rate more than four times that of White women (8.0 versus 1.9 per 100,000). In 2011, the estimated rate of HIV infection classified as stage 3 (AIDS) among adult and adolescent females in the United States was 6.0 per 100,000 population. The rate of stage 3 (AIDS) classifications among Black/African American females (32.2) was 23 times as high as the rate for White females (1.4) and more than 5 times as high as the rate for Hispanic/Latino females (5.9).

In 2011, the majority of diagnoses of HIV infection among females aged 13 years or older were attributed to heterosexual contact regardless of age group. However, the percentages attributed to heterosexual contact decreased as age group increased. An estimated 17.4% of diagnosed HIV infections among females aged 45 years and older were attributed to injection drug use, compared with 7.0% in females aged 13 to 19 years, 8.8% in females aged 20 to 24 years, 12.7% in females aged 25 to 34 years, and 14.2% in females aged 35 to 44 years.

The largest percentage of new infections in 2010 occurred among people aged 25 to 34 years (31%; 14,500), followed by those aged 13 to 24 years (26%; 12,200), and those aged 35 to 44 years (24%; 11,300). An additional 15% (7100) occurred among people aged 45 to 54 years, and 5% (2500) among those aged 55 years and older.

The increased risk of HIV acquisition in particular subpopulations is more attributable to their vulnerable social and economic situation(s) and sexual network(s) rather than their own risky behavior.[3] However, disproportionately high rates of sexually transmitted infections (STIs), including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, primary and secondary syphilis, *Trichomonas vaginalis*, and genital herpes amongst the black community may also contribute.[12]

SCREENING

Since the mid-1990s, major advances in the treatment of HIV has led to prolonged survival and improved quality of life for those living with HIV. Antiretroviral therapy (ART) during pregnancy has also led to a substantial reduction in perinatal transmission of HIV.[13] The benefits of treatment for personal health outcomes and prevention of perinatal transmission can only be achieved if one is aware of his or her HIV status. Therefore, HIV testing for the early identification of infection is essential and opt-out screening is now recommended as a component of routine management in all health care settings in the United States.[14]

A higher percentage of patients have been found to test positive in settings such as hospitals and emergency departments (2 to 7%) using HIV screening than at publicly funded HIV counseling and testing sites (1.5%) and STI clinics (2.0%) serving patients perceived at high risk for HIV.[14,15] Targeted testing on the basis of risk factors fails to identify a substantial number of people who are HIV-infected,[16–19] further supporting the recommendation for universal testing with informed consent.

The Centers for Disease Control and Prevention (CDC) recommends diagnostic HIV testing and opt-out HIV screening in all health care settings for patients aged 13 to 64 years with the onus on health care providers to initiate screening unless the prevalence of undiagnosed HIV infection in their patients has been documented as less than 0.1% (or until diagnostic yield is less than 1 per 1000 patients screened).[14] In addition, all patients initiating treatment for tuberculosis (TB) or seeking treatment for an STI should be routinely screened for HIV.[14] Routine HIV testing obviates the need for provider-dependant assessment of risk, is associated with reduced stigma and is accepted more widely by patients,[20] including women especially if they perceive that their health care provider strongly recommends the test.[21]

Providers of reproductive health care play an important role in identifying women at risk of, or infected with, HIV. These providers are particularly well suited to screen for HIV because the same issues that bring women to them, both sexual and reproductive health, provide an opportunity for discussion of potential exposure to HIV. Early diagnosis of HIV infection can have an enormous beneficial impact on the health and survival of these women along with potentially reducing risk of transmission to sexual partners and future offspring.

HIV screening should be a routine part of preconception care, providing women with maximal opportunity to know their HIV status prior to conception. A substantial proportion of the estimated 144 to 236 perinatal HIV infections per year in the United States are due to lack of timely HIV testing and treatment of pregnant women.[22,23] Multiple barriers to prenatal HIV testing have been identified[24]—health care providers' perceptions that their patients are at low risk for HIV[25,26] lack of time for counseling and testing,[25,26] lack of patient education materials,[26] lack of provider knowledge/training,[25,26] concern about managing a woman who refuses testing,[25] concern about informing a patient of his or her HIV positive status,[25] and knowledge of state regulations.[27]

Screening should be voluntary and undertaken only with the patient's knowledge and consent. Oral or written information dependant on local statutory requirements[28] should be provided to the patient and the opportunity to ask questions be facilitated. Information should be provided in clear, simple language, appropriate to the first language of the patient and interpreters should be used if required. The CDC advocates that general informed consent for medical care is considered sufficient to encompass informed consent for HIV testing and that specific signed consent for HIV testing is not required.[14] Certain states, however, may have specific requirements for counseling, written consent, confirmatory testing, or communicating HIV results and health care providers should be aware of these in case they preclude adoption of the CDC recommendations.[28,29]

In the prenatal setting, screening has proven substantially more effective than risk-based testing for detecting unsuspected maternal HIV infection and preventing perinatal transmission.[14] When offered, 75 to 95% of pregnant women accept HIV testing.[30] Universal HIV screening in early pregnancy is recommended in many resource-rich countries[31–33] and any woman with undocumented HIV status at time of labor should be screened with a rapid test if available unless she declines. On the basis of a positive rapid test result immediate initiation of

appropriate antiretroviral prophylaxis is recommended, without awaiting confirmatory testing.[13]

If the HIV status is unknown at delivery, rapid testing should be performed immediately postpartum, unless the patient declines[14] and rapid testing of the newborn should be considered so antiretroviral prophylaxis can be offered as soon as possible after birth to the HIV-exposed infant.[14]

DIAGNOSTIC TESTING

Diagnostic testing for HIV infection is composed of detecting antibodies to components of the virus, usually followed by a confirmatory test called a Western blot. At times, tests for HIV RNA or DNA may also be included in diagnostic algorithms. More recently, rapid HIV diagnostic tests have been licensed for use and are particularly relevant to the prenatal setting.

About one-third of HIV-infected patients receive their first positive diagnostic test within 1 year of an AIDS-defining illness, which implies they have been infected for approximately 7 years prior to the testing.[34] Studies show that about 41% of patients infected with HIV are diagnosed on their first test, whereas 59% are diagnosed within 1 to 2 years after an initial negative test.[35] For these reasons, it is important that those at increased and ongoing risk be advised to undergo repeat testing. From a population perspective, testing based on risk factors alone has failed to identify a large number of people with HIV infection because many individuals do not declare their risks, do not think they are at risk, or avoid testing due to stigma.[36]

In 2012, the U.S. Preventive Services Task Force (USPSTF) released preliminary recommendations for universal HIV screening among patients aged 15 to 65 years; the American College of Physicians (ACP) Guidance Statement on HIV screening similarly endorses universal screening, although they suggested the age range be expanded to 75 years, due to the growing number of HIV infections in older patients.[37,38]

Routine testing is implemented through a strategy called "opt-out testing," whereby the patient is informed orally, or in writing, that HIV testing will be performed but has the option of declining or deferring the testing.

Each HIV particle is composed of an envelope containing glycoproteins (gp120 and gp41) that surrounds the HIV RNA genome. The gp120 and gp41 glycoprotein molecules are associated with several other proteins that are essential for HIV propagation and survival; reverse transcriptase, which converts HIV RNA to DNA, and integrase, which facilitates the integration of HIV DNA into the host's cell genome. These proteins and glycoproteins evoke an immune response from the infected host.[39]

HIV-1 and HIV-2 are two related virus that can both cause AIDS in humans (see section on HIV-2 later in chapter). Multispot HIV-1/HIV-2 Rapid Test (BioRad laboratories) is a U.S. Food and Drug Administration (FDA)–approved diagnostic test used for differentiating HIV-1 from HIV-2 infection but commercially available HIV-1 viral load (VL) assays do not reliably detect or quantify HIV-2 VL.[40–42]

Antibodies to gp41 (envelope protein) and p24 antigens are the first detectable serologic markers following HIV infection.[43] The model established by Fiebig et al.[44] using plasma samples from donors, reported the window period for HIV RNA, p24 antigen, and anti-HIV antibodies as 12 days, 17 days, and 22 days, respectively. Viremia can be reliably detected within the first 2 weeks of infection with HIV and increases logarithmically during an initial "ramp-up" phase.[45] Approximately 1 month after the onset of infection, second- (IgG antibody sensitive) and third- (IgM antibody sensitive) generation immunoassays can detect early antibody responses to the virus.[45] IgG antibodies appear 6 to 12 weeks following HIV infection in the majority of patients and by 6 months in 95% of patients[46] and generally remain detectable for life. Diagnostic tests that rely on antibody alone may not detect cases of early, acute HIV infection, when the patient is most infectious. Therefore, fourth-generation immunoassays (which combine antibody and p24 antigen detection) and HIV nucleic acid amplification tests (NAATs) may be more reliable in detecting acute HIV infection.[45]

HIV screening tests can be divided into the following:

1. Antibody (+/− antigen tests)
2. Confirmatory test (Western blot)
3. Virologic tests (HIV RNA or proviral DNA)
4. Rapid tests

Most testing algorithms require the use of specific confirmatory assays, such as the Western blot, to verify reactive antibody screening test results.[47] Clear explanation should be given about the meaning of the reactive test result; emphasis should be placed on the importance of confirmatory testing and the importance of taking precautions to avoid the possibility of transmitting infection to others while awaiting results of confirmatory testing.

Antibody (+/− Antigen Tests)

The most common method of HIV screening is with an enzyme-linked immunosorbent assay (ELISA) test to detect antibodies against HIV. Results are reported as negative, positive, or indeterminate. A positive HIV test result is made based on a repeatedly positive ELISA followed by a positive Western blot. The sensitivity and the specificity of the ELISA are both greater than 99%.[48] False-negative ELISA results most commonly occur at the time between viral transmission and seroconversion during acute infection. This "window period" can last approximately 3 to 6 weeks, during which time antibody levels are not yet detectable by third-generation testing methods.[48] This window period is reduced by the fourth-generation ELISA combining detection of antibodies with HIV antigens.[49] Fourth-generation enzyme or chemiluminescent

immunoassays were engineered for dual detection of p24 antigen and HIV antibodies and can detect acute HIV infection before current standard ELISAs.[45] At the time of writing, these antigen–antibody tests were widely available in Europe and Australia, with recent introduction into Latin America but have not yet been approved by the FDA for use in the United States.[50]

The ELISA kits for screening in the United States and Europe detect all M subtypes but do not consistently detect other groups.[48] False-negative results can occur rarely in the setting of immune dysfunction due to defective humoral response or agammaglobulinemia, immunosuppression due to malignancy or medication, delay in seroconversion following early initiation of ART, or fulminant HIV infection.[48] False-positive ELISA results have been reported in patients with autoantibodies, such as autoimmune diseases, liver disease, hemodialysis, multiparity, transfusion, renal disease, or vaccinations, including those enrolled in HIV vaccine trials.[45,51]

Confirmatory Test (Western Blot)

The Western blot (WB) is the most widely accepted confirmatory assay for diagnosing HIV infection. A purified HIV antigen mixture including core (gag) (p17, p24, p55), polymerase (pol) (p31, p51, p66), and envelope (env) (gp41, gp120, gp160) proteins[48] is layered onto a gel slab and electrophoresed. These HIV antigens undergo migratory separation determined by electrical charge and molecular weight. The WB assay detects antibodies to these specific antigens and produces a colored band wherever an antigen–antibody complex is found. Reaction with a positive serum sample produces a pattern of bands characteristic for HIV. A WB is positive if reactivity is detected to gp41, p24, or gp120/160.[48] The presence of one or more bands that do not meet these criteria for a positive result is considered an indeterminate Western blot (IWB) result. The significance of IWB result varies depending on risk factors, clinical status of the patient, and the WB profile. Patients with IWB results should be retested within 1 to 3 months based on the clinicians' assessment of risk factors. They should be counseled to avoid activities that could transmit the virus until repeat testing is performed. In the setting of possible acute HIV infection, WB testing has a sensitivity of 99.3% and a specificity of 99.7%.[48]

Virologic Tests (RNA or DNA)

Other methods to establish HIV infection include viral isolation by qualitative and quantitative detection of HIV through polymerase chain reaction (PCR), branched DNA testing or nucleic acid sequence-based amplification. These tests can report the number of copies of virus per milliliter of plasma. The lower limit of detection for standard tests is 400 copies/mL, but ultrasensitive assays can detect as few as 20 to 50 copies/mL.[52] Because the tests are expensive and technically complex to perform, they have not been adopted as screening tools.[51] Viral detection, either by DNA or quantitative RNA should not be used alone for diagnosis. The use of quantitative RNA (VL) assays has not been approved by the FDA for diagnosis of HIV infection. A low positive HIV RNA level (less than 5000 copies/mL) may represent a false-positive result. Because of concerns over false-positive results, patients with HIV infection diagnosed on the basis of RNA testing should have serologic testing performed at a subsequent time to confirm seroconversion.[51]

Rapid Tests

Rapid testing is particularly helpful for those with only sporadic interactions with health care providers. Results are reported as positive, negative, or indeterminate. Six rapid HIV tests have now been approved by the FDA with sensitivities of 99.3 to 100% and specificities of 99.1 to 100%.[53]

HIV antibodies, if present, bind to HIV antigens affixed to the test strip creating a visually detectable indicator conferring a positive result. Advantages of rapid tests include point-of-care diagnosis, with preliminary results being available to the patient within minutes rather than days to weeks. Cost analyses report that rapid point-of-care testing is cheaper per test result delivered when compared with standard blood testing.[50] False-positive results have been reported in patients screened with oral fluid tests[54] and a repeatedly false-negative result has been reported in a patient with advanced HIV.[55]

A positive screening rapid test result requires confirmation with a supplemental test such as a WB. If confirmatory testing is negative or indeterminate, follow-up testing after 1 month is recommended.

As a result of the high sensitivity and specificity of rapid tests, a negative rapid test result can be disclosed to the patient as conclusive. However, retesting in 3 months' time with either a rapid test or ELISA is recommended in persons with a possible exposure within the past 3 months due to the delay in formation of detectable antibodies.[51]

The Association of Public Health Laboratories and the CDC have proposed several algorithms to allow for various combinations of screening and confirmatory tests.[14] The WHO has developed algorithms, for use in resource-constrained settings, for the definitive diagnosis of HIV infection that is composed of two or three different rapid tests in combination.[56]

Rapid Tests for HIV in Pregnancy, During Labor, and at Delivery

Ideally, all women should be screened for HIV as part of prepregnancy management so they know their HIV status prior to conception. Screening in early pregnancy enables HIV-infected women and their infants to benefit from interventions such as antiretroviral medication; scheduled cesarean delivery, if at all possible; and avoidance of breast-feeding.[14]

Although knowledge of the mother's HIV status provides opportunities for interventions that reduce perinatal HIV transmission, many women present to the health care system at the time of labor without knowledge of their HIV status.[57]

The MIRIAD Study,[58] a multicenter prospective study addressing feasibility, acceptance, and performance of rapid testing among women in labor, compared ELISA to a rapid test (Ora-Quick Rapid HIV-1 Antibody Test) in 4849 women with unknown serostatus who presented late in pregnancy or in labor. Acceptability of testing was high with 4849/5744 women (84%) agreeing to a test.[58] Of 38 women with reactive HIV rapid tests, 4 were found to be false positive, with no false-negative results when confirmed with WB.[58]

One advantage of rapid HIV tests is the potential to increase the number of individuals who are tested and receive results. Although there is the problem of false-positive results, the majority of women (HIV negative) can receive this result immediately. A recent systematic review and meta-analysis of rapid point-of-care HIV testing in pregnant women found that overall sensitivity ranged from 75 to 100% and specificity varied from 96 to 100%.[56] In four studies, a significant improvement in sensitivity and specificity estimates were reported with the use of a sequential rapid testing algorithm,[59] and one study reported parallel testing as superior to serial testing.[60]

ACUTE AND EARLY INFECTION WITH HIV

Acute HIV may present as a syndrome reminiscent of mononucleosis and include a myriad of nonspecific symptoms, such as fever, nontender lymphadenopathy, sore throat, rash, myalgia/arthralgia, and headache. Occasionally, patients may also complain of mucocutaneous ulcers. This constellation of symptoms is also known as the acute retroviral syndrome but it is not seen in all patients in the early stages of HIV infection, that is, the first 6 months after acquiring HIV. For 10 to 60% patients, the early stages of infection may be asymptomatic.[61] In patients who do have acute, symptomatic infection, the time lapse from HIV exposure to the development of symptoms is 2 to 4 weeks, although incubation periods may last longer. It is not clear if the mode of acquisition and/or quantity of viral inoculums impacts the length of the incubation period.

The presence of acute retroviral syndrome, duration of symptoms for more than 14 days, and increased severity of the symptoms, has been linked to a more rapid progression to AIDS and poorer prognosis; in one study of 218 female sex workers with well-documented seroconversion dating, each additional symptom at the time of acute infection was associated with an increasing risk of overall mortality.[62–64]

Fatigue, myalgia, and fever ranging from 38 to 40°C are the most common symptoms in the acute HIV infection phase. A rash may erupt 48 to 72 hours after the fever starts and usually lasts for 5 to 8 days. The rash typically involves the upper half of the chest, neck, and face, although the scalp, palms, and soles may also be affected. The macular or maculopapular lesions are usually small (5 to 10 mm), well-circumscribed, ovoid, and pink to deep red. In some cases, vesicular or pustular lesions may be noted. Nontender adenopathy involving the axillary, cervical, and occipital nodes are common. Although the nodes will decrease in size over time, a modest degree of enlargement usually persists. Mild hepatosplenomegaly may be noted. Patients often complain of a sore throat and there may be edema and hyperemia of the pharynx; enlargement or exudates on the tonsils is not common. Painful mucocutaneous ulcers involving the mouth, esophagus, genitals, or anus is a distinctive manifestation of acute HIV infection. Gastrointestinal (GI) symptoms such as nausea, diarrhea, anorexia, and weight loss are common. Headaches are usually retroorbital and eye movement may intensify the pain.

Acute HIV infection is a period of rapid viral replication and infection of CD4 T cells, and VLs may be quite high, for example, more than 100,000 up to more than 1 million copies/mL; there may be a transient decline in the CD4 cell count. Leukocyte and lymphocyte counts vary during the acute infection, and initially, the total white blood cell (WBC) count may drop, but as the number of lymphocytes expands, the WBC count will increase. CD8+ lymphocytes increase at a faster rate than CD4+ T lymphocytes, and this results in a persistent inversion of the CD4 to CD8 ratio that is less than one.

The diagnosis of acute HIV infection is established by the detection of HIV viremia, either through a viral RNA or p24 antigen test, in the setting of a negative or indeterminate HIV serologic test pattern in a patient with clinical features suggestive of the acute retroviral syndrome. Detectable viremia does not develop until approximately 10 to 15 days after infection, and even the most sensitive immunoassays do not become positive until 5 days after that. The reverse transcriptase polymerase chain reaction (RT-PCR) test is not approved by the FDA for HIV RNA detection in the evaluation for early HIV infection but it is highly sensitive and specific. A false-positive test should be suspected if the VL is low (less than 10,000 copies/mL) in the presence of acute retroviral syndrome symptoms. If this occurs, a repeat sample should be drawn and if it too is positive, this is suggestive of a true positive result.[65] The p24 antigen becomes positive approximately 5 to 7 days following the detection of viral RNA.[66,66a] After a diagnosis of acute or early HIV infection is made, patients should ideally be referred to a provider with experience in HIV management.

Some HIV-infected patients (4 to 7%) remain asymptomatic over many years (more than 10 years) without ART and are referred to as "long-term nonprogressors."[67] "Elite controllers" are HIV-seropositive individuals who are not on therapy but have no evidence of viremia, as measured by standard assays (either less than 50 or less than 75 copies/mL), and maintain high CD4 cell counts. "Viremic controllers" have low levels of detectable viremia.

FACTORS AFFECTING PROGRESSION OF HIV INFECTION

The average life expectancy for a HIV-infected patient in the absence of treatment is approximately 10 to 12 years, although the rate of HIV progression varies greatly between individuals in the absence of ART. The CD4 count and plasma VL are two important and independent laboratory determinants of the rate of progression of HIV infection. Of the two, the CD4 cell count is the strongest predictor of disease progression and survival.[68] The average rate of CD4 cell decline or CD4 slope is about 50 cells/mm^3 per year and the average viral burden (without therapy) is 30,000 to 50,000 copies/mL.

Genetic regulation of immunologic control of HIV and medication adherence are the two most important factors in the rate of disease progression, although other factors that negatively impact progression have been identified (Table 27.1). As CD4 cell counts decline, the risk of OIs increases. Various CD4 count thresholds are used to determine when prophylaxis for various OIs, such as *Pneumocystis* pneumonia (PCP), toxoplasmosis, *Mycobacterium avium* complex (MAC) infection should be initiated.

There are now four treatment strategies that are known to prolong survival:

- ART
- *Pneumocystis carinii* prophylaxis
- *M. avium* prophylaxis
- Care by a physician with HIV-care experience

PRIMARY HIV CARE

The focus of this section is to illustrate general principles of evaluation and establish a basic template for evaluation of the HIV-infected woman. It is beyond the scope of this chapter to discuss clinical staging of HIV and manifestations of various OIs; however, comprehensive guidelines regarding aspects of care of HIV-infected persons are widely available.[69]

TABLE 27.1 Factors That Influence the Rate of Progression of HIV Infection

- Demographics—increasing age at the time of HIV infection is associated with more rapid progression to AIDS in the absence of ART
- Calendar year of infection—infections at various time frames/years appear to progress at different rates and this may be due to emerging changes in the circulating virus and changes in pathogenicity
- Symptoms during primary HIV infection—symptomatic primary HIV infection portends a faster progression
- Viral characteristics—some viruses appear to be attenuated compared to others
- Viral replication capacity—the fitness of a virus appears to be determined in part by the ratio of replication of a mutated strain compared to a wild-type reference strain; a lower replication capacity may be associated with a slower progression
- HIV subtype—there are three distinct groups of HIV-1 called M, N, and O, although only M is globally found; various subtypes or clades in group M (clades a–J) vary in immunogenicity, replication kinetics, transmission patterns, and pathogenesis; subtype D may be more virulent than other subtypes
- Use of coreceptors—HIV uses the chemokine coreceptors CCR5 and CXCR4 to enter human lymphocytes and HIV isolates are classified as either CCR5 tropic (R5), CSCR4-tropic (X4) or dual tropic (R5/X4 strains); R5 viruses predominate in primary infection and X4 types may emerge later in infection and are more virulent and are able to replicate more efficiently, hence they are associated with disease progression; a phenotypic tropism assay is recommended by major consensus committees prior to initiation of therapy with CCR5 antagonists, because these drugs are not active against X4 or dual-mixed tropic viruses
- Viral phenotype—during HIV infection, about half of the patients will develop syncytium-inducing (SI) viruses and the presence of SI HIV variants is associated with more rapid disease progression
- Immune escape—the loss of CD8 cell responses against specific HIV epitopes is associated with clinical progression of infection
- Dual HIV infection—zero infection with more than one strain of HIV is associated with more rapid disease progression
- Genetic background of infected patient—different HLA genotypes appear to be linked with rapid progression to AIDS such as A24, B35, B37, B56, B58S, and A1-B8-DR3; other HLA types may be associated with long-term nonprogression (B57, B27, B14, and C8)
- Coinfection with other pathogens—other infections may influence and increase the rate of HIV progression, for example, CMV, HSV, TB, syphilis
- Nutritional status—weight loss is associated with HIV progression but it is not clear if it is a marker or a cause for progression
- Injection drug use—injection drug use may affect HIV disease progression, possibly through poor medication adherence and issues with access to care
- Alcohol—alcohol depresses levels of CD4 counts

ART, antiretroviral therapy; HLA, human leukocyte antigen; CMV, cytomegalovirus; HSV, herpes simplex virus; TB, tuberculosis.

From Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe. *Lancet*. 2000;355:1131–1137; Dorrucci M, Rezza G, Porter K, et al. Temporal trends in postseroconversion CD4 cell count and HIV load: the Concerted Action on Seroconversion to AIDS and Death in Europe Collaboration, 1985–2002. *J Infect Dis*. 2007;195:525–534; Barbour JD, Hecht FM, Wrin T, et al. Higher CD4+ T cell counts associated with low viral pol replication capacity among treatment-naive adults in early HIV-1 infection. *J Infect Dis*. 2004;190:251–256; Baeten JM, Chohan B, Lavreys L, et al. HIV-1 subtype D infection is associated with faster disease progression than subtype A in spite of similar plasma HIV-1 loads. *J Infect Dis*. 2007;195:1177–1780; Poveda E, Briz V, Quiñones-Mateu M, et al. HIV tropism: diagnostic tools and implications for disease progression and treatment with entry inhibitors. *AIDS*. 2006;20:1359–1367; Goetz MB, Leduc R, Kostman JR, et al. Relationship between HIV coreceptor tropism and disease progression in persons with untreated chronic HIV infection. *J Acquir Immune Defic Syndr*. 2009;50:259–266; Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. *J Infect Dis*. 2006;194:926–930; Koot M, Keet IP, Vos AH, et al. Prognostic value of HIV-1 syncytium-inducing phenotype for rate of CD4+ cell depletion and progression to AIDS. *Ann Intern Med*. 1993;118:681–688; Kemal KS, Beattie T, Dong T, et al. Transition from long-term non-progression to HIV-1 disease associated with escape from cellular immune control. *J Acquir Immune Defic Syndr*. 2008;48:119–126; Markowitz M, Mohri H, Mehandru S, et al. Infection with multidrug resistant, dual-tropic HIV-1 and rapid progression to AIDS: a case report. *Lancet*. 2005;365:1031–1038; Brumme ZL, Brumme CJ, Chui C, et al. Effects of human leukocyte antigen class I genetic parameters on clinical outcomes and survival after initiation of highly active antiretroviral therapy. *J Infect Dis*. 2007;195:1694–1704; Schwarze-Zander C, Blackard JT, Zheng H, et al. GB virus C (GBV-C) infection in hepatitis C virus (HCV)/HIV-coinfected patients receiving HCV treatment: importance of the GBV-C genotype. *J Infect Dis*. 2006;194:410–419; Schacker T, Zeh J, Hu H, et al. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *J Infect Dis*. 2002;186:1718–1725; Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS*. 2004;18:2075–2079; Podlekareva D, Mocroft A, Kirk O, et al. Fungal infection as a risk factor for HIV disease progression among patients with a CD4 count above 200/microl in the era of cART. *Scand J Infect Dis*. 2008;40:908–913; Celentano DD, Galai N, Sethi AK, et al. Time to initiating highly active antiretroviral therapy among HIV-infected injection drug users. *AIDS*. 2001;15:1707–1715; Samet JH, Cheng DM, Libman H, et al. Alcohol consumption and HIV disease progression. *J Acquir Immune Defic Syndr*. 2007;46:194–199.

For the majority of women of reproductive age, a visit for a routine annual exam or gynecologic problem may be the only opportunity for HIV testing and assessment of the potential gynecologic manifestations of HIV. Thus, reproductive health care providers are in a unique position to both diagnose and manage these complications. The prevalence and incidence of gynecologic problems are high in HIV-infected women.[70–72]

Due to the medical and social complexity of HIV, a multidisciplinary approach to care is essential. The primary care provider is often best suited to perform the initial evaluation and coordinate referrals to specialty providers. Better clinical outcomes have been reported in patients managed by an experienced HIV medical provider.[73–75] The importance of continuing gynecologic follow-up should also be emphasized because a large number of women still do not receive gynecologic care from their HIV specialist.[76] During the initial evaluation, assessment of support systems should be made for each patient and clear, nonjudgmental communication, sensitivity, and confidentiality are essential.

Clinical Assessment of HIV

A comprehensive evaluation of the HIV-infected woman includes a thorough history and physical examination, including pelvic exam, laboratory tests, and psychological and social support assessment.[69,77]

History (HIV Specific)

- Date of diagnosis; prior negative test results
- Possible routes of exposure
- HIV-related symptoms/OIs
- HIV-associated complications and comorbidities; malignancies, cardiovascular disease history/risk
- Lowest CD4 cell count documented
- Previous antiretroviral or prophylactic therapies; duration of treatment, side effects or complications, response, results of resistance testing, adherence
- HIV-related symptoms including fever, night sweats, weight loss, headaches, visual changes, oral thrush/ulceration, respiratory symptoms, diarrhea, skin rashes, changes in neurologic function/mental status.

History (Other Medical)

- Chronic medical conditions; for example, peripheral neuropathy, GI disease, chronic viral hepatitis, renal impairment, bone disease
- Previous TB/TB exposure

History (Gynecologic)

- Menstrual history
- Sexual practices
- Contraception
- Condom use history
- Previous sexually transmitted and other genital tract infections
- Prior abnormal Pap smears
- Other gynecologic illnesses or symptoms

History (Medications/Allergies/Vaccinations)

- Current medication—including prescription/over-the-counter/dietary or herbal supplements
- Allergies—hypersensitivity to previous therapies, including sulfonamides
- Vaccination history, including tetanus toxoid/pneumococcal vaccine/hepatitis A and B vaccines

History (Social and Family)

- Drug and alcohol use
- Support systems
- Disclosure history
- Current employment
- Relationship status
- Child care responsibilities
- Depression and domestic violence screening

Physical Examination (General)

- General appearance; vital signs, height, weight
- Skin—check for any rashes, for example, seborrheic dermatitis, Kaposi sarcoma, folliculitis, fungal infections, psoriasis
- Body habitus—drug-related lipodystrophy
  - Fat accumulation—increased dorso-cervical fat pad, gynecomastia, abdominal protuberance (visceral fat)
  - Lipoatrophy—loss of subcutaneous fat in the face, extremities, or buttocks
- Fundoscopy—refer to ophthalmologist for review in those with advanced HIV (CD4 less than 50 cells/mm^3) and those with ocular symptoms.
- Oropharynx—check for thrush (candidiasis), oral hairy leukoplakia, mucosal Kaposi sarcoma, aphthous ulceration, periodontal disease.
- Cardiopulmonary examination
- Abdominal exam—examine for hepatomegaly or splenomegaly.
- Persistent generalized lymphadenopathy; localized lymphadenopathy, hepatomegaly or splenomegaly
- Neurologic examination—perform a general assessment of mental status, cognitive function, coordination, memory, and motor and sensory testing (there is an HIV dementia scale available if the exam suggests HIV-associated dementia).
- Breast examination

Physical Examination (Pelvic)

- Visual inspection of vulva and perineum—genital ulcers, warts, or other lesions
- Speculum examination—look for abnormal vaginal discharge, vaginal/cervical lesions.
- Bimanual and rectovaginal examination—rule out cervical, uterine, adnexal, and rectal tenderness/masses.

Pelvic examination should be performed annually. This may be performed more frequently if there is a history of abnormal Pap smears, unsafe sexual practices, exposure to STIs or development of gynecologic signs or symptoms. STI screening should be performed when the patient reports recent or ongoing high-risk sexual activity. Pelvic examination every 6 months may be considered in women with clinically advanced disease, low CD4 cell counts, and/or high VLs because their incidence of certain HIV-related gynecologic problems may be increased.[77]

Laboratory

Patients found to be infected with HIV should also be screened for exposure to or latent infection with other infections (Table 27.2).

An assessment of the woman's immunologic and virologic status should be done on a regular basis. Any patient with a CD4 count less than 200 cells/mm^3 should be assessed for primary OI prophylaxis according to guidelines.[78] Patients should be referred to an HIV specialist for consideration of ART and long-term virologic follow-up.

Selected Primary Care Issues and HIV Infection

Approximately 30% of HIV-infected patients in the United States are coinfected with hepatitis C virus (HCV), and about 8% are coinfected with hepatitis B virus (HBV).[79] Liver disease tends to progress more rapidly in patients with HCV and HBV concurrently infected with HIV/HCV compared with those with HCV or HBV infection alone. Some ART therapies have both anti-HIV and anti-HBV activity.[80]

Despite lower rates of obesity among HIV-positive women, the rates of hyperglycemia are almost double that of HIV-negative women, particularly among HIV-infected Hispanic and Black women.[81,82] As a result, diabetes must be considered in the preventive care HIV-infected women receive.

TABLE 27.2 Screening for Other Infectious Diseases

- Syphilis
- Gonorrhea and chlamydia infection
- Trichomoniasis
- PPD testing or TB interferon gamma testing should be done in all HIV-infected patients, except those with prior TB or a positive PPD. Annual retesting should be considered in patients with a negative test who are at continued risk for TB exposure. Retesting is also warranted following ART that results in a significant rise in CD4 count as the previous "negative" test may have simply been due to anergy.
- Toxoplasma IgG antibody titer (to identify patients at potential risk for reactivation infection)
- CMV IgG antibody titer for those at low risk of infection. CMV seronegative patients with HIV infection should receive CMV-negative or leukocyte-reduced blood products if they are necessary.
- Varicella-zoster virus (VZV) IgG antibody titer (for those without a history of chickenpox)

PPD, purified protein derivative; TB, tuberculosis; ART, antiretroviral therapy; IgG, immunoglobulin G; CMV, cytomegalovirus.

There is a greater risk of coronary artery disease in HIV-infected patients, especially for those on protease inhibitors, which increase the likelihood of developing glucose intolerance and/or dyslipidemia.[83] If coronary artery disease is diagnosed, management should be initiated according to accepted practices.

HIV infection is a very significant risk factor for reactivation of latent TB, and patients with a positive PPD are at high risk for developing active infection in the absence of prophylaxis. HIV infection is also associated with accelerated progression of TB and extrapulmonary involvement.

HIV-infected patients should be advised to avoid eating raw eggs, unpasteurized dairy products, raw seafood, and undercooked meat.

Immunizations

In general, immunizations should also be given according to current CDC guidelines.[84] All inactivated vaccines are acceptable to use with HIV infection, but live-attenuated vaccines should be avoided, although some live vaccines (e.g., varicella) are recommended in HIV-infected patients with CD4 cell counts greater than 200 cells/mm^3. Close contacts of HIV-infected patients should receive all age-appropriate immunizations with the exception of oral polio and smallpox vaccines.

Pneumococcal pneumonia and meningitis are leading causes of morbidity and mortality among HIV-infected patients, and because of the increasing incidence of drug-resistant pneumococcal strains, it is getting harder to treat them. The most important risk factor for developing pneumococcal infections is the level of immunosuppression (e.g., CD4 count less than 200 cells/mm^3). All HIV-infected patients with a CD4 count greater than 200 cells/mm^3 should receive pneumococcal vaccine. If the CD4 count is lower, the vaccine may not be as effective. Revaccination should be considered 5 years after the initial vaccination or sooner if it was administered when the CD4 count was less than 200 cells/mm^3 and the CD4 count is greater than 200 cells/mm^3 on ART.

All HIV-infected patients should receive influenza vaccination annually. The inactivated vaccine formulation is recommended; intranasal vaccines should not be used in immunosuppressed patients.

The hepatitis B vaccination series should be administered to all HIV-infected patients who do not have serologic evidence of current or prior HBV infection. Due to a reduced response rate to the vaccine in HIV-infected patients, a postvaccination hepatitis B surface antibody (HBsAb) titer is recommended 1 to 6 months after the series is completed. Revaccination should be considered for those who lack evidence of serologic response to the initial series.[85]

Hepatitis A vaccination should be administered to patients with specific risk factors early in the course of HIV infection or after immune reconstitution with ART.

The response to the polysaccharide meningococcal vaccine is suboptimal among patients with HIV but it should be given to HIV-infected adults with functional or anatomic asplenia, travel exposure, are of college age, or living in dormitories. HIV-infected individuals should receive two doses, with the second dose administered 8 weeks or more after the first dose, plus booster doses every 5 years.

The American Academy of Pediatrics recommends the MMR vaccine be given to HIV-infected patients, except those who are severely compromised, whereas Advisory Committee on Immunization Practices (ACIP) recommends that only HIV-infected patients with CD4 counts greater than 200 cells/mm^3 should receive it.[86,87]

Because there is a risk of disseminated TB disease after vaccination, and the efficacy of BCG vaccine is unknown, BCG immunization is not recommended in HIV-infected patients.

HIV IN ADOLESCENTS

Adolescents and young adults accounted for approximately one-fourth of new HIV infections in 2010, and approximately one-third of new infections in adolescents occur in females.[88] The number of HIV-infected adolescents who acquired their infection perinatally is also increasing and it is important to recognize that the needs of these adolescents are quite unique. The primary mode of HIV acquisition in adolescents is through high-risk sexual behavior.

Pretest counseling of adolescents needs to include a discussion that if the initial test is negative, there is still a need to retest if the reason for the testing is risky behavior. Understanding the adolescent's psychological level of maturation and any issues they may have as well as their social and economic support systems will be critical to developing successful treatment and prevention plans. Generally, an adolescent can seek HIV testing and treatment without the consent of a parent but it is helpful to discuss with them who they would rely on if the test were positive. Risk reduction strategies should be included in any pretest counseling session.

Ideally, the same person who did the pretest counseling will also discuss the results with the adolescent in a private and secure setting. If the test is negative, reinforcement on risk reduction and plans to protect themselves from HIV should be given. If the test is positive, close follow-up should be scheduled and the patient should be asked if he or she would like assistance in disclosing the results to trusted adults and/or partners.

One of the biggest issues in treating HIV-infected adolescents is compliance with ART. Poor adherence increases the risk of viral resistance as well as viral rebound. Psychosocial factors play an important role in adherence so evaluating the adolescent for comorbidities such as mental illness or substance abuse, developmental issues, their ability to manage complex schedules of drugs, their living situation, and a source of adult support is very important.

The physical exam and lab testing should determine the Tanner stage of development (which will help determine drug dosing), screening for other STIs, a Pap smear, and serology screening for varicella. If they are negative for varicella immunity, then immunization is indicated but as it may temporarily increase VL, it should be given after VL testing is done.

Treatment should be given by an expert in the care of adolescents with HIV.

TREATMENT OF HIV

All patients with early HIV infection should undergo drug resistance testing, regardless of whether treatment is going to be started or not as 15 to 20% of patients may be infected with an isolate carrying at least one drug resistance mutation and some mutations become undetectable over time[89–92] (Table 27.3).

There are two types of HIV resistance tests available. Genotypic testing identifies specific resistance mutations in the individual's HIV genome and is interpreted using rule-based algorithms. Phenotypic testing is a measure of the ability of the patient's virus to replicate in the presence of specific antiretroviral drugs and may be the preferred test in patients who are highly treatment-experienced with a history of multiple resistance mutations. Phenotypic testing is more expensive than genotypic testing.

If treatment is initiated (immediately or later), the selection of treatment regimens should take into account any initially detected resistance mutations. Drug resistance may be specific to a particular drug and not

TABLE 27.3 Contributing Factors to HIV Drug Resistance

- Biology of HIV—HIV reverse transcriptase is responsible for replicating the viral genome and is error prone; combined with high rates of replication, this leads to the frequent occurrence of randomly generated genetic mutations, some of which confer drug resistance
- Genetic barriers to resistance—resistance to a drug may be achieved via a single mutation (i.e., there is a low genetic barrier to resistance), whereas other drugs require multiple mutations for resistance to occur; resistance to 3TC or non-nucleoside reverse transcriptase inhibitors usually appears earlier than resistance to most protease inhibitors
- Regimen potency—continued viral replication in the presence of a drug may lead to an accumulation of mutations and, ultimately, drug resistance, even in drugs with a high genetic barrier to resistance
- Pharmacokinetics of antiretroviral drugs—low serum trough concentrations of drugs, including protease inhibitors, may allow for virus with low levels of resistance to continue to replicate, accumulate more mutations, and ultimately result in drug resistance; this is offset through the use of pharmacokinetic "boosting" with ritonavir; drug–drug interactions that lead to subtherapeutic levels of ART drugs may also promote drug resistance; pharmacokinetic variability between patients may also impact the development of resistance
- Medication adherence—nonadherence is associated with incomplete viral suppression and the development of drug-resistant HIV viral variants

3TC, lamivudine; ART, antiretroviral therapy.

necessarily an entire class and in some instances, resistance to one drug may increase susceptibility or decrease susceptibility to another drug.[93,94] The use of phenotypic and phenotypic susceptibility testing leads to better viral suppression and has been associated with better survival.[95,96] A specialist experienced in the management of HIV infection and interpretation of drug resistance testing should be consulted.

HIV treatment guidelines from the U.S. Department of Health and Human Services (DHHS) and the International Antiviral Society-USA (IAS-USA) panels now recommend antiretroviral treatment in all patients with HIV infection, regardless of CD4 cell counts.[68,97] Once started, ART is continued indefinitely. Clinicians are not able to accurately assess which patients will be adherent to ART regimens, so patients should not be denied ART based solely on a history of psychiatric illness or chaotic lifestyles.

The initiation of ART can lead to a microbe-specific inflammatory response called the "immune reconstitution inflammatory syndrome" or IRIS, among those with undiagnosed OIs, for example, pulmonary TB or cryptococcal meningitis. For this reason, a complete review of systems should be performed, particularly in the patient with advanced AIDS. Shortly after starting ART, patients with underlying cytomegalovirus (CMV) retinitis may develop immune recovery vitreitis, a condition characterized by a decline in visual function.

There are six major classes of drugs used to treat HIV infection and over 20 antiretroviral medications within these classes (Table 27.4). An ART regimen is described as having a "backbone" and a "base." The backbone typically consists of two nucleoside reverse transcriptase inhibitors (NRTIs). The base has traditionally included either a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI), although raltegravir, a drug from the integrase inhibitor class is also a possible base option. ART regimens should have at least three active antiretroviral medications; regimens with more than three drugs are not more efficacious and are associated with more side effects.[98] Regimens with three different classes of drugs are no more potent than regimens made up of two different classes of drugs[99] (Table 27.5).

Nucleoside analogs, or NRTIs, are considered the backbone of ART and are generally used in combination with an NNRTI, PI, or integrase inhibitor. NRTIs are usually given in pairs, such as tenofovir and emtricitabine, abacavir and lamivudine, and zidovudine and lamivudine.[97] All of these combinations are available as coformulations; Truvada (tenofovir-emtricitabine), Combivir (zidovudine-lamivudine), and Epzicom (abacavir-lamivudine), respectively, which helps to reduce pill burden and improve drug adherence. The DHHS guidelines panel recommends tenofovir-emtricitabine as the preferred nucleoside analog coformulation in combination ART for the treatment-naive patient because of its overall potency, favorable toxicity profile, and convenience of dosing.[68] Tenofovir-emtricitabine is also the preferred agent for HIV-infected patients with concomitant hepatitis B virus infection.

TABLE 27.4 Classification of Antiretroviral Drugs

Drug (Abbreviations)	Brand Name
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	Ziagen
Didanosine (ddI)	Videx, Videx EC
Emtricitabine (FTC)	Emtriva
Lamivudine (3TC)	Epivir
Stavudine (d4T)	Zerit
Tenofovir (TDF)	Viread
Zalcitabine (ddC)	Hivid
Zidovudine (ZDV, AZT)	Retrovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Delavirdine (DLV)	Rescriptor
Efavirenz (EFV)	Sustiva
Nevirapine (NVP)	Viramune
Rilpivirine (RPV)	Edurant
Protease inhibitors (PIs)	
Amprenavir (APV)	Agenerase
Atazanavir (ATV)	Reyataz
Darunavir (DRV)	Prezista
Fosamprenavir (FPV)	Lexiva
Indinavir (IDV)	Crixivan
Lopinavir/ritonavir (LPV/r)	Kaletra
Nelfinavir (NFV)	Viracept
Ritonavir (RTV)	Norvir
Saquinavir (SQV)	Fortovase, Invirase
Tipranavir (TPV)	Aptivus
Fusion inhibitor	
Enfuvirtide (T-20)	Fuzeon
Integrase inhibitors	
Elvitegravir (EVG)	(investigational)
Dolutegravir (DTG)	(investigational)
Raltegravir (RAL)	Isentress
CCR5 antagonist	
Maraviroc (MVC)	Selzentry
Fixed-dose combinations	
Zidovudine + Lamivudine	Combivir
Zidovudine + Lamivudine + Abacavir	Trizivir
Lamivudine + Abacavir	Epzicom
Emtricitabine + Tenofovir	Truvada
Efavirenz + Emtricitabine + Tenofovir	Atripla
Rilpivirine + Emtricitabine + Tenofovir	Complera
Elvitegravir + Cobicistat + Emtricitabine + Tenofovir	Stribild

Ritonavir is a potent inhibitor of the hepatic enzyme CYP (450) 3A4. This characteristic is used to "boost" the serum concentration of other PIs, which improves their trough serum concentrations and rates of viral suppression; use of ritonavir also enables lower dosing of the parent drug, thereby decreasing pill burden for the patient. When used at doses of 400 mg/day, ritonavir is not viewed as an active ingredient in any ART regimen,

TABLE 27.5 Guidelines for Antiretroviral Therapy Regimens for Initial Treatment of HIV Infection

A non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, plus two nucleoside reverse transcriptase inhibitors (NRTIs)

OR

- A boosted protease inhibitor (PI): atazanavir-ritonavir once daily or darunavir-ritonavir once daily plus two NRTIs

OR

- An integrase inhibitor, raltegravir (400 mg twice daily) with two NRTIs
- The recommended NRTI coformulation is tenofovir-emtricitabine in all of the above combinations.

From U.S. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuideLineID=7&ClassID=1. Accessed December 5, 2013.

TABLE 27.6 Special Considerations for Use of Antiretrovirals With Women

ARV Issues for Women	Considerations
ARV adverse effects	Some ARV adverse effects may be more severe in women: • Anemia (zidovudine) • Lactic acidosis (particularly with stavudine + didanosine) • Neuropathy (stavudine, didanosine) • Hepatotoxicity (nevirapine) • Severe rash (non-nucleoside reverse transcriptase inhibitors [NNRTIs], darunavir, tipranavir) • Abacavir hypersensitivity • Lipoaccumulation: central fat accumulation in breasts, abdomen; lipoatrophy: face • Bone loss, especially after menopause
Pregnancy	Teratogenicity: • Efavirenz is associated with neural tube defects in women with exposure during the first trimester; should be avoided in pregnant women during the first trimester, and in women who may become pregnant Pharmacokinetic (PK) changes: • Serum levels of some ARVs may be decreased during pregnancy (e.g., unboosted protease inhibitors [PIs], lopinavir/ritonavir, ritonavir) • Some ARVs should be avoided and certain ARVs may require dosage adjustment in the third trimester • PK studies in pregnancy are not available for some ARVs
Contraception	There are significant interactions between some hormonal contraceptive agents and certain ARVs

ARV, antiretroviral.
From Richardson S. Health care of HIV-infected women through the life cycle. http://hab.hrsa.gov/deliverhivaidscare/clinicalguide11/cg-404_women_life_cycle.html. Accessed December 5, 2013.

it is only a pharmacokinetic booster for other drugs. Full doses of ritonavir (600 mg/day twice a day) are associated with too many adverse events for it to be a mainstay of ART. Using ritonavir as a booster is associated with adverse effects such as hyperlipidemia, drug interactions, and GI intolerance; these effects are dose related.

Studies have shown that ART regimens based on NNRTIs or ritonavir-boosted PIs, with a backbone of two NNRTIs are comparable for the treatment of HIV.[97]

The management of ART is complex and should be delivered by providers with specific training. One study, done in the mid-1990s demonstrated a 31% reduction in the risk of death when HIV-infected patients were treated by physicians with a great deal of clinical experience with this disease.[100]

Adverse Effects of Antiretroviral Therapy

ART drugs are extremely potent and are known to be associated with adverse effects ranging from mild to life-threatening. Some reports suggest that ART drugs may evoke different treatment responses in women compared to men, and there are some considerations when treating women with HIV, for example, differences in risk for treatment complications, drug–drug interactions, tolerability, and the possibility of pregnancy (Table 27.6).[101-103] General intolerance to ART agents appears to be more common in women than men and leads to increased discontinuation rates. Women are at greater risk for the syndrome of rash and hepatic failure with nevirapine, a higher incidence of rash with efavirenz, and higher risk for lactic acidosis with some nucleoside analogs, especially stavudine and didanosine.[61,104,105]

Body shape changes may occur during ART due to lipodystrophy; this may be seen as fat atrophy (thinning of the cheeks, extremities, or buttocks) or increased fat deposition (visceral or cervicodorsal areas). Stavudine is most commonly implicated in lipoatrophy while the PI class is associated with lipodeposition with some exceptions (e.g., atazanavir or darunavir). Management consists of modifying the antiretroviral drug regimen, although reversal of the process may be gradual although some patients use various modes of plastic surgery or aesthetic procedures for correction.

Dyslipidemia is a relatively common adverse effect of treatment with ART regimens, including PIs as well as NNRTIs. Management of dyslipidemia consists of lifestyle modification, consideration of switching to a more "lipid friendly" regimen if possible, and pharmacologic treatment with statins and/or fibrates.

Peripheral neuropathy, which is mainly sensory and involves the lower extremities, has been reported with didanosine and stavudine, as well as with HIV infection alone. If it occurs, the causative ART agent should be discontinued and an alternative drug used; pharmacologic therapy should be considered for patients who remain symptomatic despite modification of ART.

Mitochondrial toxicity has been described in association with NRTIs as a result of their interference with the function of DNA polymerase. The clinical manifestations of mitochondrial toxicity include lactic acidosis, pancreatitis, myopathy, and hepatic steatosis.

Asymptomatic mild to moderate lactic acidemia is common in patients on regimens that include NRTIs but does not predict the occurrence of severe lactic acidosis. Routine monitoring of serum lactic acid is not recommended in the absence of symptoms. However, a venous lactate level should be obtained in a patient on NRTIs who presents with unexplained weight loss, nausea, vomiting, or abdominal discomfort.

Hepatotoxicity can occur with any antiretroviral drug but has been reported most often with NNRTIs and PIs. Fulminant hepatic toxicity has been most commonly seen with nevirapine, especially in women with a higher CD4 count. Because of this association, nevirapine should be avoided in women with a CD4 count greater than 250 cells/mm^3 and in men with a CD4 count greater than 400 cells/mm^3.

Nephrotoxicity can occur with tenofovir and indinavir. A Fanconi-like syndrome with hypophosphatemia, glycosuria, and hypokalemia, as well as a nonanion-gap metabolic acidosis has been described with tenofovir.

Efavirenz-containing regimens have shown teratogenicity in primate studies and there have been reports of neural tube defects during early gestational exposure, with the greatest risk occurring during the first trimester, although the evidence is not conclusive.[106] The FDA has categorized efavirenz as category D, but it can be used after the first trimester; in select cases, for example, there is intolerance to alternative agents, known drug resistance, or drug–drug interactions limit available options.

PREVENTION OF TRANSMISSION

Transmission of HIV can occur via sexual contact, exposure to blood through sharing of injection drug use paraphernalia, receipt of contaminated blood/tissue and exposure to body fluids such as breast milk. Vertical transmission can also occur and is addressed later in this chapter. Transmission events appear to be more frequent from patients with acute HIV infection and late-stage disease (i.e., AIDS) compared with chronic infection; these observations are probably linked to the high levels of viremia that are seen during early and late infection.[107]

HIV-infected patients should be counseled that they must not donate blood or body organs and should avoid exposure to others of their blood or body fluids. Practices that should be avoided include sharing needles, toothbrushes, or razors that may be contaminated with blood. Ordinary household exposure does not lead to the transmission of HIV, and no special precautions need to be taken for cleaning dishes or laundry.

Sexual Transmission

Transmission of HIV through sexual contact accounts for the vast majority of HIV cases worldwide. Information regarding this mode of transmission is vital not only to women already infected, but also to women who test negative for HIV but engage in high-risk behavior. Infectiousness and susceptibility may be influenced by multiple factors, including direction of transmission (male-to-female versus female-to-male versus female-to-female), type of sexual act, VL, male circumcision, and STIs (chlamydia, gonorrhea, herpes simplex virus [HSV] infection, human papillomavirus [HPV] infection, and/or syphilis) in the index case or partner.[108] The overall risk of infection by male-to-female vaginal intercourse has been estimated to be 1 in 200 to 1 in 2000, and by female-to-male vaginal intercourse has been estimated to be between 1 in 700 and 1 in 3000.[109]

Women and their partners should be educated about how to reduce sexual transmission. The major strategies for reducing the sexual transmission of HIV focus on four main areas: encouraging the use of condoms, early diagnosis and treatment of STIs, cART, and reducing the amount of unsafe sexual behavior by promoting abstinence, by delaying sexual intercourse, or by decreasing the number of sexual partners.

A Cochrane review published in 2002 revealed that male condom effectiveness is approximately 80%,[110] but when used consistently, their effectiveness can be as high as 95%.[111] Female condoms have also been shown to be an effective barrier against transmission of STIs, including HIV in laboratory testing,[111] but have remained relatively unpopular since their introduction.[112] Patients should be encouraged to use condoms not only to prevent the transmission of HIV, but also to prevent the transmission of STIs, which enhance the risk of HIV transmission.

Male circumcision has been demonstrated to result in a minimum 60% reduction in HIV acquisition.[113] Studies assessing the effect of male circumcision in transmission from HIV-infected men to their female partners have produced conflicting results.[114] It however remains an important preventive strategy for HIV transmission globally.[115,116]

STI increases the transmission of HIV by increasing the viral burden in the genital tract and by increasing susceptibility to HIV,[117] especially those that are ubiquitous (HSV-2, trichomoniasis), produce lifelong infection (HSV-2) and/or produce ulcers (HSV-2, syphilis).[118] This underscores the importance of detection and treatment of STIs in the prevention of HIV; however, prevention strategies such as daily suppressive treatment of HSV-2 in people with established HSV-2 infection has failed to reduce HIV acquisition.[119]

Topical antimicrobial products for prevention are currently being assessed. In vitro studies have shown that spermicides, such as nonoxynol-9 (N-9), inactivate HIV within 60 seconds; however, in vivo studies have yielded disappointing results.[120] A Cochrane review assessing N-9 for preventing vaginal acquisition of STIs by women from men, demonstrated that N-9 provides no protection against STIs and was associated with higher rates of HIV acquisition and higher rates of genital ulceration.[120]

A recent systematic review of published randomized controlled safety trials of vaginal microbicides, apart from N-9, found that most trials were of short duration, with limited numbers of participants and demonstrated few significant differences between the active and control arms.[121] Recently, tenofovir gel has been shown to be both safe and effective for the prevention of HIV infection in women.[122] The success with tenofovir gel holds promise as a future female controlled method of HIV prevention after many years of disappointing results.[123]

Combination ART can reduce the quantity of virus present in the blood and genital tract,[124] although discordant results have been reported.[125] The effect of ART on VL in the female genital tract of women does not appear to be as rapid or reliable as in males[126] and may be affected by collection method and menses.[127]

A large number of couples are "serodiscordant" for HIV with only one partner being HIV-infected. A recent meta-analysis assessing the sexual transmission of HIV according to VL and ART in heterosexual serodiscordant couples observed no transmission in partners where the HIV-infected partner was treated with ART and had a VL less than 400 copies/mL.[128] However, data was insufficient to calculate rates according to the presence or absence of STIs, condom use, or vaginal or anal intercourse.[128] The choice of antiviral agents also impacts the concentration of HIV in genital secretions. Most agents can penetrate the genital tract; however, PIs achieve limited concentrations in genital secretions.[129]

In 2008, Switzerland's Federal AIDS Commission concluded, after review of four studies assessing HIV transmission in serodiscordant couples, that seropositive individuals were not at risk of transmitting HIV to a seronegative partner if their VL was undetectable in the blood for at least 6 months, they adhered strictly with their antiretroviral regimen, and they did not have other STIs.[130] In contrast, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the WHO recommends a comprehensive package of HIV prevention strategies, including correct and consistent condom use, reiterating that an undetectable HIV load has not been proven to completely eliminate the risk of transmission.[131]

Despite counseling, transmission of HIV within discordant couples may still occur. Two meta-analyses of controlled trials assessing information, motivation, and behavioral intervention in people living with HIV demonstrated a reduction in risk-taking behavior with regards to unsafe sex.[132,133] A recent review by Fisher et al.[134] addressing secondary prevention of HIV infection found that prevention intervention by trained clinical and nonclinical staff (counsellors) in and out of clinical care settings, resulted in reduced sexual risk behavior in multiple studies. This illustrates the importance of HIV detection and counseling strategies to reduce the likelihood of future transmission. One study in a resource poor setting did not find an increase in high-risk sexual behavior in the setting of cART.[135] This has also been reported in a meta-analysis of the effect of ART on sexual behavior in developed countries.[136] Importantly, however, the likelihood of unprotected sex was higher, regardless of serostatus, in people who perceived that receiving cART or having an undetectable VL therapy protects against transmission of HIV.[136]

Postexposure Prophylaxis

Postexposure prophylaxis (PEP) is often recommended following potential sexual exposure to HIV. Observational data suggest that PEP is approximately 80% effective in preventing HIV seroconversion.[137] The per-contact risk of transmission from sexual exposure varies according to the nature of exposure. The estimated risks for receptive vaginal intercourse and insertive anal intercourse are 0.1 to 10.0%; 1 to 30% with receptive anal intercourse and 0.1 to 1.0% with insertive vaginal intercourse.[137] Good risk estimates are lacking for oral intercourse, and although considered to pose a lower risk of transmission,[137] there are case reports of HIV acquisition in patients whose only reported risk factor was oral intercourse.[138,139] The risk of acquiring HIV after rape by an unknown assailant depends on many factors specific to the assault.

Consensus guidelines recommend PEP in people exposed to a known HIV-infected source and to selected high-risk populations with unknown HIV status among whom the seroprevalence of HIV infection is considered sufficient to justify the toxicity and cost of treatment.[140] Clinicians in the United States may seek expert telephone advice through the National HIV/AIDS Clinician's Consultation Center, 24 hours a day (1-888-448-4911).

After exposure, the HIV status of the exposed person should be determined; if rapid testing is not available the initial assumption is that they are not HIV-infected and PEP may begin until standard antibody tests are available. PEP is not offered, however, to people who repeatedly engage in high-risk behaviors because this may lead to intermittent, but sequential courses of ART dosing. If the source is known to be HIV positive, it is helpful if they are willing to provide their treatment history and recent VL test results because this may assist in determining which PEP regimen to choose.

Optimally, a course of nonoccupational PEP should begin as soon as possible after exposure and within 72 hours of exposure as the window of opportunity to interrupt HIV dissemination is narrow. PEP is not indicated if the patient presents more than 72 hours after exposure. Baseline testing for HIV, HBV, and HCV in the exposed should be performed along with testing of the source if possible.[140]

Uncertainty remains regarding the optimal PEP regimen, although many regimens consist of three drugs.[99,141] Two possible regimens are tenofovir-emtricitabine (coformulated as Truvada) PLUS raltegravir or tenofovir-emtricitabine (coformulated as Truvada)

PLUS ritonavir-boosted atazanavir or ritonavir-boosted darunavir.[61] These regimens may be used in pregnancy. Tenofovir-emtricitabine is well tolerated and requires only once a day dosing. Raltegravir has higher concentrations in the genital tract than PIs and NNRTIs, although it does require dosing twice a day. Atazanavir and darunavir are well tolerated and less likely to cause issues with lipids than other PIs but they do require boosting with ritonavir; they are given as single daily doses. Because of issues with side effects, neither nevirapine nor abacavir should be used for nonoccupational PEP.

Reported rates of adherence to PEP medication are generally 70 to 80%.[99] Most patients prematurely stop treatment due to adverse effects or toxicity. An important determinant of acceptance of PEP is the strength of the recommendation and support of its use by the provider seeing the patient.[142]

Follow-up testing after baseline testing should be done at 4 to 6 weeks, 12 weeks, and 6 months after the exposure. Most of the patients who will seroconvert do so within the first 3 months. Factors associated with seroconversion despite the use of PEP include delayed administration of medication (more than 45 hours after exposure), receptive anal intercourse, nonadherence to treatment, and repeated exposures.[143] For those whose exposure histories represent no significant risk for HIV transmission or who seek medical care more than 72 hours after potential nonoccupational HIV exposure, the use of PEP is not recommended as potential side effects associated with antiretroviral medications are likely to outweigh the potential benefits.[140]

Women potentially exposed to HIV should use condoms or practice sexual abstinence in the first 6 to 12 weeks after exposure; avoid donating blood, plasma, organs, or tissues for approximately 89 weeks; and if they are breast-feeding at the time of the exposure, a discussion about the risks and benefits of continuing to do so while on the PEP regimen should be had. They should be informed about the symptoms consistent with primary HIV infection and if they develop these, should undergo HIV RNA testing. (Routine testing for this is not warranted usually as there is a risk of a false-positive test result.)

GYNECOLOGIC ISSUES

Many of the topics in this section are addressed in more detail in other chapters of this textbook, so the focus in this chapter is to present the information specific to the HIV-infected woman. The areas covered include contraception, menstrual abnormalities, STIs, lower genital tract neoplasias, and menopause.

Contraception

Knowledge of contraceptive methods for family planning and prevention of STIs is of paramount importance to health care providers looking after HIV-infected women and women at risk of HIV infection. Unfortunately, methods that prevent conception may not necessarily prevent HIV transmission, and the most effective means of preventing HIV infection is not necessarily the ideal contraceptive method. Any discussion of contraception with women must address two issues: prevention of unintended pregnancy and prevention of acquisition or transmission of HIV and other STIs. In recommending a contraceptive method, the provider must consider its effectiveness, side effects, contraindications, convenience of use, and cost. With the HIV-infected woman, potential for drug interactions (particularly with antiretrovirals) must also be considered. Studies in the United States, France, and Russia reveal that barrier methods are the most commonly used method of contraception amongst HIV-infected women, hormonal methods are less commonly used, and intrauterine devices are rarely used.[144]

Condoms

Condom effectiveness for preventing pregnancy is estimated at 90.7 to 98.6%.[110] A Cochrane review published in 2002 assessing condom effectiveness in reducing heterosexual HIV transmission found an 80% reduction in HIV incidence with condom use.[110] Condom failure can occur because of incorrect condom usage, breakage or slippage, and/or method/device failure.[110] Consistent condom use is defined as using a condom for all acts of penetrative vaginal intercourse. When used consistently and correctly, latex condoms are highly effective against preventing transmission of HIV and reducing the risk of other STIs.[145] A meta-analysis showed that condom use does not prevent genital HPV infection but may result in decreased condyloma or high-grade cervical disease.[146] It is important to identify which women are at increased risk for poor condom use and counsel them appropriately. Risk factors for poor condom use include exchanging sex for money or drugs, alcohol binge drinking, having limited financial resources, and being dependent on one's partner.[147]

Intrauterine Devices

Among HIV-infected women using intrauterine devices (IUDs), there is no increased risk of overall complications or infectious complications when comparing HIV-infected with noninfected women.[148] Therefore, in 2004, the WHO changed their position on the use of IUDs in HIV-infected women as increasing evidence demonstrated their safety in this population.[149] Studies in women with HIV have found no increased risk of HIV disease progression, including changes in CD4 cell count, HIV RNA levels and survival, with intrauterine contraceptive use.[110] However, this same study reported an increased risk of declining CD4 cell count and death among users of hormonal oral contraceptives or

depot medroxyprogesterone acetate (DMPA) use compared with IUD users.[150,151] The WHO recommends that women with AIDS should not undergo insertion of IUD unless they are well on cART.[149] Continuation of IUD use, in women with AIDS, if already in situ and not associated with complications, can be considered in patients clinically well on cART with close monitoring.[149]

Hormonal Contraception

Oral contraceptive methods are known to be effective in preventing pregnancy, but several issues need to be considered when prescribing them to HIV-infected women. These include their impact on HIV transmission, their effect on HIV disease progression and potential drug interactions with antiretrovirals.

Oral hormonal contraceptive use may increase the risk of HIV transmission by its association with cervical ectopy and thereby HIV shedding or by its effect on lowering the vaginal pH.[152] However, oral hormonal contraception may also reduce transmission by reducing menstrual bleeding and increasing cervical mucous viscosity.[152] Several studies have investigated the effect of hormonal contraception on HIV acquisition, often with conflicting results.[153–156]

Most studies including a recent systematic review assessing safety of hormonal contraception suggest no increased risk of HIV disease progression with hormonal contraceptives, when assessing CD4 cell count, VL, or survival.[150,157]

Progesterone-only contraceptives include progestogen-only pills, levonorgestrel or etonogestrel implants (LNG/ETG) and DMPA/norethisterone enanthate (NET-EN). Studies of DMPA have reported inconsistent findings with regards to increased risk of HIV acquisition, effect on HIV-1 VL and disease progression.[158–164]

Antiretroviral drugs can interact and potentially increase or decrease the bioavailability of hormonal contraceptives. Hormonal contraception is metabolized by the cytochrome p450 pathway. Drugs which induce enzymes in this pathway may potentially reduce the efficacy of the hormonal contraception. NNRTIs and ritonavir-boosted PIs have this potential interaction so use of barrier methods for contraception is recommended when taking these drugs. Nucleoside analogs and raltegravir do not seem to impact oral contraceptive levels of hormones or their efficacy.

Nonoral administration of contraceptive steroids in women on cART may minimize pharmacologic interactions. A recent study looked at changes in DMPA with the use of nelfinavir, nevirapine, or efavirenz and demonstrated no effect of these antiretrovirals on the concentration of the hormone.[165] The use of cART in combination with parenteral administration of hormonal contraceptives, including the contraceptive vaginal ring or patch, injectable NET-EN and etonogestrel, and the levonorgestrel IUD, requires further study.

For detailed, up-to-date information regarding HIV drug interactions, consultation of an external resource such as the HIV Drug Interactions website: www.hiv-druginteractions.org is recommended.

Menstrual Dysfunction

Small studies suggest that HIV-infected women may experience higher rates of menstrual irregularities, including amenorrhea, menorrhagia, and intermenstrual bleeding, although many of these reports are prior to cART and have not been confirmed in all studies.[166–168] Given the increased risk of cervical malignancy and STIs in HIV-infected women, these conditions should be excluded as potential etiologies. Retrospective and prospective studies have shown inconsistent associations between HIV serostatus and amenorrhea in the absence of severe disease or weight loss.[169–171] A large prospective study comparing HIV-seropositive and HIV-seronegative women controlling for body mass index (BMI), substance use and age, found very low prevalence of amenorrhea, with no difference between the two groups.[169] However, a trend toward shorter cycles with greater cycle variability was noted in HIV-infected women with high VL and low CD4 counts.[169] In the absence of wasting or severe immunosuppression, the workup of amenorrhea in an HIV-infected woman should be similar to that in the general population.

Abnormal Cervical Cytology/Human Papillomavirus

HIV-infected women have a high prevalence of coinfection with HPV, persistence of HPV, and abnormal cervical cytology.[152,171–175] There are more than 100 serotypes of HPV of which at least 13 are considered oncogenic, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66, and some studies have suggested a higher prevalence of oncogenic genotypes in HIV-infected women.[171] The use of cART has not led to clearance of HPV in cervical samples and recent studies have shown little impact of cART on the incidence of cervical lesions.[176–178] HIV-associated immunosuppression may play a role in the progression of lesions from low grade to high grade; however, its role in progression to invasive cancer remains less clear.

Because of this, recommendations for cervical screening in HIV-infected women are different from those for HIV-uninfected women. The Infectious Diseases Society of America (IDSA) recommends all HIV-infected women have a cervical Pap smear performed at the commencement of care, repeated at 6 months, and if results are normal, annually thereafter.[69] Women with atypical squamous cells on Pap smear should undergo colposcopy and directed biopsy, with further testing as

indicated.[69] The British HIV Association and the CDC recommends all abnormal smears should be referred to a specialist colposcopy service, and that management of cervical intraepithelial neoplasia (CIN) should not differ from the general population.[179,180]

The role of HPV testing as an adjunct to Pap testing in HIV-infected women is not clearly defined. Combined testing with both HPV DNA testing and Pap tests has recently been recommended as an acceptable alternative primary screening approach in the general population by multiple organizations but has not yet been recommended by the DHHS.[180] No recommendations exist regarding the use of HPV testing for triage of HIV-infected women older than age 30 years with normal cervical cytology—to guide more or less frequent Pap testing, or in follow-up of CIN after treatment.[180]

A recent large prospective study demonstrated that the absence of oncogenic HPV is associated with a low incidence of squamous cell intraepithelial lesions in HIV-infected women with CD4 greater than 500 cells/mm^3 over a 3-year period.[181] The incidence was comparable to the seronegative population raising the possibility of applying the same cervical screening practice to both groups. This strategy requires further evaluation.

HPV vaccines are now available and can protect against infection with HPV subtypes 6 and 11 (the subtypes most often associated with genital warts) and HPV subtypes 16 and 18 (responsible for approximately 70% of cervical cancers). Although safety, efficacy, data, and long-term durability in this population is not well-established, the vaccines are not live virus vaccines and therefore can be used in HIV-infected women as recommended by the IDSA and CDC.[69,84]

Anal Squamous Cell Carcinoma

Anal squamous cell carcinoma (SCC) is associated with high-risk subtypes of HPV (e.g., 16 and 18), and among HIV-infected women, the incidence for anal cancer is 7 to 28 times greater than the general population.[182] Other risk factors for anal neoplasia include multiple sexual partners, history of STIs, smoking, unprotected vaginal or anal intercourse, and organ transplantation.[183]

A recent multisite study of HIV-infected women found the prevalence of anal HPV infection to be higher than cervical HPV infection (80% compared with 45%, respectively), and the prevalence of anal intraepithelial neoplasia (AIN) was 16%.[184] However, there is a lack of data from randomized controlled trials at this time to guide recommendations for anal cytology screening.

Vaginal and Vulvar Cancer

Routine screening for vaginal cancer in HIV-infected women posthysterectomy for benign disease is not recommended.[180] Women with a past history of high-grade CIN or invasive cervical cancer are at increased risk and should receive a regular vaginal cuff Pap test. Women with HIV have an increased incidence for vulvar intraepithelial neoplasia (VIN), although cART may decrease the risk of developing VIN.[185] As for the general population, there is no screening procedure available for vulvar cancer. HIV-infected women with a past history of cervical or vaginal cancer should have inspection of the vulva with or without colposcopy as part of regular follow-up.[180]

Breast Cancer

A recently published study found no significant increase in the incidence of breast cancer in HIV-infected women compared with the general population,[186] although atypical presentations and rapid progression of disease have been reported.[187,188] IDSA recommends that screening mammography in HIV-infected women follow standard guidelines:

1. Mammography should be performed annually in women aged older than 50 years.
2. In women aged 40 to 49 years, providers should perform individualized assessment of risk for breast cancer and inform them of the potential risks and benefits of screening mammography.

Menopause

With improved survival associated with cART, more women are reaching an age associated with menopause. By 2015, 50% of HIV-infected individuals in the United States are likely to be aged 50 years and older.[189] Although there is some evidence to suggest that HIV-infected women may be more likely to undergo premature physiologic menopause, there is currently no conclusive data describing any significant differences in age of menopause in HIV-infected women compared with HIV-uninfected women.[190]

With an anticipated increase in the number of HIV-infected women experiencing hormonal changes of menopause in the future, the impact of this on other comorbidities such as osteoporosis needs to be considered. A meta-analysis assessing osteoporosis and HIV found that the odds ratio for osteoporosis in HIV-infected patients compared to seronegative controls was 3.7.[191] The odds of osteoporosis were 2.4 times greater in those receiving cART compared with ARV-naïve controls.[191] Those on PIs were 1.6 times more likely to have osteoporosis compared to non–PI-treated controls.[191]

Other risk factors for low bone mineral density (BMD) in HIV-infected people include low BMI, advanced age, female gender, high VL, advanced stage of disease,[192] low muscle mass, low testosterone levels,[193] and duration of illness.[194] Smoking,[195,196] non-Black/White ethnicity,[197]

stavudine or tenofovir exposure,[198] steroid exposure,[195] and duration of NRTI exposure[196] have also been associated with low BMD in HIV-infected patients.

Due to the frequency of bone density abnormalities, the IDSA recommends baseline bone densitometry be performed in postmenopausal women older than 65 years of age and in younger postmenopausal women with more than one risk factor for premature bone loss.[77]

Use of bisphosphonates is effective at increasing BMD in HIV-infected patients but outcome data pertaining to fracture rates in this population is lacking.[199–203] Bisphosphonate therapy should be considered in HIV-infected women with osteopenia along with advice regarding regular weight-bearing exercise, adequate calcium and vitamin D intake—with replacement as necessary and cessation of cigarette smoking and excessive alcohol intake.

Vaginal and Cervical Infections in the HIV-Infected Woman

Vaginal and cervical infections are discussed in detail in other chapters of this textbook. This section will focus specifically on the prevalence, natural history, effect on transmissibility of HIV, and management considerations in the HIV-infected woman.

STIs have been associated with increased shedding of HIV in cervical-vaginal secretions.[204] A recent systematic review and meta-analysis assessing genital tract infections and HIV reveal that STIs differ substantially in their impact on HIV shedding in the genital tract.[205] Because heterosexual and most cases of perinatal transmission occur through direct contact with virus in the genital tract, the presence of these infections has significant clinical implications. It has been hypothesized that lower genital tract infections cause mucosal inflammation, resulting in the disruption of the normal epithelium leading to increased amounts of HIV shedding.[206] Treatment of cervicitis, as well as vaginal infections, has been shown to decrease the shedding of HIV in cervical-vaginal secretions by three- to six-fold.[204]

Treatment of vaginal and cervical infections is the same as for HIV-uninfected women.

Bacterial Vaginosis

Bacterial vaginosis (BV) is a polymicrobial clinical syndrome caused by replacement of normal H_2O_2-producing *Lactobacillus* sp. in the vagina with high concentrations of anaerobic bacteria (*Prevotella* and *Mobiluncus* sp.), *Gardnerella vaginalis*, and *Mycoplasma hominis*. It is rare in women who have never been sexually active, raising the possibility that BV is associated with a sexually transmitted pathogen.

BV appears to be more prevalent and more persistent among HIV-infected women and women with CD4 counts less than 200 cells/mm^3 are more likely to have both persistent and severe BV than those with CD4 counts greater than 500 cells/mm^3.[207] Standard treatment regimens are recommended for HIV-infected women with BV and routine treatment of sexual partners is not recommended.[208]

BV has been estimated to be the most prevalent vaginal infection, particularly in countries with high HIV prevalence.[207] Factors associated with BV include alcohol use, smoking, multiple sexual partners, a new sexual partner, douching, and lack of vaginal lactobacilli.[209] A recent meta-analysis indicated that BV increased the risk of HIV acquisition by approximately 60%.[210]

Trichomoniasis

Trichomonas vaginitis is caused by the protozoan *T. vaginalis*. It can result in asymptomatic disease or fulminant symptoms. There is no correlation between HIV-related immunosuppression and incidence, persistence, or recurrence.[208] *T. vaginalis* has been shown to increase the risk of HIV acquisition, and if HIV-infected, there has been a reported increased risk of infection with *T. vaginalis*.[211] Sexual partners of patients with *T. vaginalis* should be treated[208] because it has been shown to be a significant risk factor for transmission between discordant couples. *T. vaginalis* has been associated with adverse outcomes in pregnancy in HIV-uninfected women such as preterm delivery and low birth weight[212] but pregnancy outcome data in HIV-positive women infected with *T. vaginalis* is limited. All pregnant women should receive counseling regarding the potential risks and benefits of treatment. HIV-positive women should receive the same treatment regimens as those who are HIV-negative.[208]

Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is caused predominantly by *Candida albicans*. Vaginal colonization rates are higher among HIV-infected women compared with HIV-uninfected women with similar demographic characteristics and high-risk behavior.[208] The rate of colonization and symptomatic VVC correlates with increasing severity of immunosuppression. Despite *Candida* vaginitis being more frequent in HIV-infected women, it does not appear to be of increased clinical severity.[213] A recent meta-analysis indicated that the odds of HIV detection in the female genital tract are significantly increased in the presence of VVC.[205] The treatment of VVC in HIV-infected women should follow management guidelines for the general population.[208]

Cervicitis

Cervicitis is a common inflammatory condition of the cervix. *C. trachomatis* and *N. gonorrhoeae* are the causative organisms in less than half of cervicitis

cases; the remaining cases are referred to as nonchlamydial, nongonococcal cervicitis or nonspecific cervicitis.[214] Cervicitis can also be associated with trichomoniasis and genital herpes (especially primary HSV-2 infection).

Cervicitis is thought to play an important role in the transmission of HIV, both by increasing susceptibility to HIV infection and increasing HIV viral shedding.[205] Several mechanisms are proposed that promote both susceptibility and increased viral shedding. These include increased viral replication in the setting of infection or inflammation, disruption of normal mucosa, and increased numbers of HIV-infected cells in cervical secretions. Effective treatment of chlamydial or gonococcal cervicitis has been shown to correlate with a greater than six-fold decrease in cervical HIV RNA level and with normalization of cervical polymorphonuclear counts.[204]

Cervicitis can be a sign of upper genital tract infection (endometritis). Women who present with cervicitis should be assessed for pelvic inflammatory disease and tested for *C. trachomatis* and *N. gonorrhoeae* with NAAT.

Presumptive therapy for cervicitis should be given for women at increased risk (younger than age 25 years, multiple sexual partners, unprotected sex), especially if follow-up cannot be arranged. Concurrent therapy for *N. gonorrhoeae* is recommended if prevalence is greater than 5% in the patient population.[208] Women with recurrent or persistent cervicitis should be re-evaluated for re-exposure to STIs and relapse/reinfection of STI should be excluded.

Sexual partners should be notified and examined for STIs for which the index patient received treatment and abstinence from sexual intercourse is recommended until therapy is completed to avoid reinfection.[208]

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) in HIV-infected women may have an atypical presentation, require surgical intervention and early studies suggested that PID in HIV-infected women may be[215–219] associated with an increased mortality rate. Women with HIV experience similar symptoms when compared with seronegative controls although may be more likely to have complications such as tubo-ovarian abscess.[220,221] Treatment recommendations are the same as they are for women uninfected of HIV.[208]

Genital Ulcer Disease

Genital ulcers are often seen in HIV-infected women and it may be difficult to determine the etiology. The most common causes of genital ulcer disease (GUD) among HIV-infected women are HSV and syphilis, although often no etiology is identified.[222] It is important to consider advanced immunosuppression or failure of cART in women with severe disease. Women with idiopathic GUD should also have a careful examination of the oral cavity because nearly 40% will also have oral aphthous ulcers.[222] A recent study assessing the effect of GUD on HIV coreceptor expression in the female genital tract showed that women with either syphilis, HSV-1, or HSV-2 infection have significantly higher numbers of CD14+ cells expressing chemokine receptor 5 (CCR5) within the genital ulcer.[223] This increased expression may account for increased HIV transmission in the setting of GUD.[223]

Syphilis facilitates both the transmission and acquisition of HIV infection.[224,225] All patients with a new diagnosis of syphilis should be tested for HIV.[208] Approximately one-quarter of HIV-infected patients present with lesions of primary and secondary syphilis at diagnosis.[226] Those with CD4+ cell counts of less than 200 cells/mm^3 are at higher risk of a reduced serologic response to syphilis which improves with cART treatment.[227] HIV-infected patients should receive the same treatment regimens as seronegative patients.[208] Concurrent HIV infection is associated with an increased risk of neurologic complications and higher rates of treatment failure with current therapeutic recommendations.[228] Due to the frequency of cerebrospinal fluid (CSF) abnormalities in HIV-infected patients, it is recommended by some specialists that those with early syphilis undergo lumbar puncture and CSF examination prior to receiving therapy for syphilis.[208] If the initial lumbar puncture reveals abnormalities then follow-up CSF examination is recommended.[208] For early syphilis, clinical and serologic review is recommended at 3, 6, 9, 12, and 24 months after therapy to detect treatment failure. Those who meet the criteria for treatment failure (signs and symptoms that persists or recur, or four-fold increase in nontreponemal test titer) should receive repeat CSF examination and retreatment (as recommended for HIV-negative patients). CSF examination and retreatment should be considered in those whose nontreponemal test titers do not decrease four-fold within 6 to 12 months of therapy. Patients with early latent syphilis should be managed as per recommendations for HIV-negative patients with primary and secondary syphilis and patients with late latent syphilis or syphilis of unknown duration should have CSF examination before treatment. For late latent syphilis or syphilis of unknown duration, clinical and serologic follow-up at 6, 12, 18, and 24 months should occur post-therapy and those with clinical symptoms or a four-fold rise in nontreponemal titers should have repeat CSF and retreatment if indicated. If nontreponemal titer does not decline four-fold, CSF examination should be repeated and treatment administered.[208]

All pregnant women should be screened for syphilis at their first prenatal appointment. Reactive treponemal screening tests should be confirmed with nontreponemal

tests and treatment is recommended at the time of diagnosis during pregnancy. Populations with a high prevalence or those individuals at high risk should have serologic testing performed twice during the third trimester (at 28 weeks' gestation and delivery). Penicillin is effective for preventing maternal transmission to the fetus and for treating fetal infection. Women who are penicillin allergic should be desensitized and treated with penicillin.

Worldwide, 50 to 90% of HIV-infected people are also infected with HSV-2.[229] Both the risk of HIV acquisition and the risk of HIV transmission are higher if the person is infected with HSV-2.[230,231] Disruption of mucosa in the setting of genital ulcers favors acquisition of HIV by providing a portal of entry.[231] In addition, reactivation of HSV-2 causes mucosal infiltration with activated CD4 lymphocytes, which serve as target cells for HIV attachment.[232] Immunosuppressed patients have more frequent recurrences and can develop more severe disease, with deep ulcerative genital and perianal lesions.[233] The presence of a herpetic lesion for more than 1 month duration should raise the possibility of immunosuppression and the person should be offered an HIV test.

HSV shedding is increased in HIV-infected patients. ART has been shown to reduce the severity and frequency of symptomatic genital herpes, but frequent subclinical shedding still occurs.[234] Suppressive or episodic therapy with oral antiviral medication is effective in decreasing clinical manifestations of HSV in HIV-infected people.[235–237] Long-term use of acyclovir as suppressive therapy for up to 10 years in HIV-infected patients has been found to be safe and effective with no significant interactions with cART.[238] Acyclovir resistance is more prevalent in immunocompromised patients.[239] HSV resistance testing should be performed if lesions recur or persist in a patient receiving antiviral treatment.[240]

The risk of perinatal HSV transmission from an infected mother is high (30 to 50%) in women who acquire genital herpes near the time of delivery compared with women with a history of recurrent herpes, where the risk of perinatal transmission is less than 1%.[208] Preventing acquisition of genital HSV infection during late pregnancy and avoiding exposure of the infant to herpetic lesions during delivery are important strategies to reduce perinatal HSV transmission.

The few published studies that have assessed vertical transmission of HIV in HSV-infected pregnant women have yielded inconsistent results. Three studies demonstrated an increased risk of neonatal HIV transmission in women with HSV[241–243]; however, a recent case control study reported an absence of association between vertical HIV transmission and HSV-2 coinfection.[244] Management of pregnant HIV-infected women with HSV should be discussed with an infectious diseases specialist.

REPRODUCTIVE OPTIONS IN WOMEN WITH HIV

Prepregnancy

All HIV-infected women and discordant couples should undergo discussion and counseling regarding options for parenthood and reproduction.[245] Preconception counseling should include discussion regarding effective contraception to reduce the likehood of unintended pregnancy.[245] Women should be counseled about the implications HIV infection may have on any future pregnancy including the risk of mother-to-child HIV transmission and interventions to reduce this risk such as ART, mode of delivery, and avoidance of breast-feeding.

HIV infection can be transmitted from mother to child in utero, during labor and delivery and postpartum, through breast-feeding. The risk of perinatal transmission, in the absence of intervention is approximately 25%.[246]

Women should be counseled regarding reduction in perinatal transmission risk with cART, prior to initiation or modification of ART, with avoidance of potentially teratogenic agents.[246]

An evaluation of the need for OI prophylaxis and administration of influenza, pneumococcal, rubella, varicella, and hepatitis A and B virus vaccine should be made. Both partners should be screened for genitourinary tract infections and appropriately treated.

Preconception counseling should include a discussion of issues specific to HIV infection, but in addition, should include issues common to all women such as diet, weight, vaccination status, illicit drug use, alcohol, smoking and folic acid supplementation to reduce the incidence of neural tube defects.[247] Control of comorbid medical conditions such as diabetes and hypertension should be achieved prior to conception and may require referral to relevant medical specialists for optimal care.

Patients should be screened for depression and appropriately referred for optimal care.

Achieving Pregnancy

Reproductive Counseling for HIV Serodiscordant Couples Where the Woman Is HIV-Infected With an Uninfected Male Partner

When the discordant couple comprises an HIV-infected woman and seronegative male, self-insemination with the partner's semen eliminates the risk of male acquisition of HIV. To maximize the success of cycle, tracking the use of ovulation kits is recommended. Ovulation kits detect the luteinizing hormone surge just prior to ovulation and may assist in facilitating timed insemination. In the event of multiple unsuccessful attempts at conception, fertility of both partners should be assessed including a semen analysis and female assessment for tubal patency.

Reproductive Counseling for HIV Serodiscordant Couples Where the Man Is HIV-Infected With an Uninfected Female Partner

Assisted conception techniques have been used in Europe and the United States to minimize the risk of HIV transmission from HIV-seropositive men to their HIV-negative partners by sperm washing and either intrauterine insemination or in vitro fertilization/intracytoplasmic injection of sperm (ICSI). Observational data has confirmed this to be a safe and effective technique.[248–251]

Prevention of Mother-to-Child Transmission of HIV

Mother-to-child transmission (MTCT) of HIV can occur in utero, intrapartum, and postpartum through breast-feeding. Interventions for prevention of mother-to-child transmission (PMTCT) of HIV have an essential role in reducing the incidence of HIV globally. In developed countries, interventions have reduced the rate of vertical transmission less than 2%.[252,253] Pregnant women are at increased risk for acquiring HIV during pregnancy, so repeat HIV testing in the third trimester is recommended for those without HIV infection.

Maternal VL has been found to be a strong independent determinant of the risk of MTCT of HIV. Other risk factors for transmission (some of which have only been reported prior to the use of cART) include advanced maternal disease, low CD4+ cell count, young maternal age, history of stillbirth, chorioamnionitis, prolonged rupture of membranes, sexually transmitted diseases, vaginal delivery, events associated with increased bleeding (episiotomy, perineal laceration, intrapartum hemorrhage), and breast-feeding.[254–261]

Antiretroviral drugs can reduce MTCT of HIV by:

1. Reducing viral replication and lowering maternal plasma VL
2. Pre-exposure prophylaxis in the fetus by placental transfer
3. PEP of neonates after delivery

The risk of perinatal transmission in women with undetectable HIV RNA levels appears to be extremely low but has been reported for all levels of maternal HIV RNA.[262] Therefore, antiretroviral prophylaxis is recommended for all pregnant women even those with a very low, or undetectable VLs, or no therapy.[205] Although these women are at low risk for clinical disease progression, use of cART to reduce plasma RNA to undetectable levels significantly reduces the risk of perinatal transmission and likewise reduces the need to consider elective cesarean section.[246]

Treatment should consist of two nucleoside analogs and either a ritonavir-boosted PI or a non-nucleoside analog. Unless contraindicated, for example, drug resistance or anemia, zidovudine (ZDV) should be included in ART regimens in pregnant women. Didanosine and stavudine, alone or in combination, should be avoided in pregnancy due to the increased risk of hepatotoxicity. Nevirapine should not be given to women with CD4+ counts greater than 250 cells/mm^3 unless the benefits outweigh the risks for toxicity. Once daily dosing of lopinavir-ritonavir is not recommended in pregnancy as adequate drug levels may not be reached. In the third trimester, the levels of some PIs may be reduced.

Women already receiving cART should continue on their current regimen even if it does not include ZDV or lopinavir-ritonavir, as long as it is tolerated and it is successfully suppressing viral replication, although efavirenz should be avoided during the first trimester.[246] It is not necessary to add ZDV to the regimen if it is not already being taken.

CD4 counts should be measured every 3 months in pregnancy and HIV RNA levels should be assessed 2 to 6 weeks after initiation or change in therapy, then monthly thereafter until VL levels are undetectable, then at least every 2 months.[263] Levels should be measured at 34 to 36 weeks' gestation to optimize mode of delivery planning. First-trimester ultrasound is recommended to confirm dates of gestation, thus allowing a more accurate estimation of delivery date. Repeat ultrasound is recommended at 18 to 22 weeks' gestation to assess fetal anatomy.[263]

Combination therapy with three or more drugs is recommended[246] and should be made in consultation with an HIV-specialist. Physiologic and pharmacodynamic changes that occur during pregnancy may affect the pharmacokinetics of antiretrovirals necessitating a change in dose. PIs appear to be the most commonly affected class.[246] Recent studies conducted outside of the United States demonstrate differing pharmacokinetics in different ethnic populations, suggesting there may not be a generalized need for increased dosing of boosted PIs during the third trimester of pregnancy.[264,265]

Intrapartum intravenous ZDV is recommended for all HIV-infected women, unless contraindicated due to hypersensitivity. The recommended dose is 2 mg/kg loading dose administered over 1 hour followed by 1 mg/kg/hour until delivery. The other components of the patient's cART regimen should be continued orally, at the usual dosing schedule even if this is during labor except for stavudine, which should not be administered concurrently with ZDV due to antagonism.[246] During labor, invasive fetal monitoring, that is, fetal scalp electrodes, operative deliveries with vacuum devices or forceps, artificial rupture of membranes, and prolonged rupture of membranes (no labor progress after 4 hours) should be avoided.

Four to 6 weeks of neonatal ZDV chemoprophylaxis is recommended to all HIV-exposed infants.[246,266] The benefit of adding other antiretrovirals (3TC + NVP) to the neonatal regimen is uncertain.

The benefit of elective cesarean section (ECS) in women receiving cART, with low VLs, remains unclear.[252,253] A Cochrane review assessing the efficacy and safety of cesarean delivery for prevention of MTCT of HIV found limitations to the early studies addressing this topic. ECS was found to be efficacious among HIV-infected women not taking antiretrovirals during pregnancy or taking only ZDV. Postpartum morbidity (including febrile morbidity, urinary tract infection, endometritis, thromboembolism) is higher in those undergoing ECS, compared with those undergoing vaginal delivery, but lower than those undergoing nonelective cesarean section (including emergency procedures).[267] Risk of postpartum morbidity was increased among women with advanced HIV disease (lower CD4 counts and higher VLs) and comorbid medical conditions such as diabetes.[267] More recent studies have not consistently shown significant differences between women undergoing ECS compared with vaginal delivery when adjusted for VLs or cART use.[252] The American College of Obstetricians and Gynecologists recommends that women with detectable virus levels greater than 1000 HIV RNA copies per milliliter should undergo scheduled cesarean section at 38 weeks' gestation,[268] whereas guidelines from the Europe recommend an elective cesarean section in women with a VL greater than 50 copies/mL.[266] Insufficient data exist regarding women with VLs that are detectable but less than 1000 copies/mL, and management decisions should be made on an individual basis.[246]

Transmission of HIV through breast milk poses a significant problem globally, as the majority of HIV-infected women live in conditions where exclusive formula-feeding is not affordable, sustainable, or safe. Increased risk of transmission via breast-feeding has been associated with higher maternal breast milk VLs, lower CD4 counts duration of breast-feeding, cracked nipples or breast abscesses, and younger maternal age with higher parity.[268–272] Mixed breast-feeding has also been associated with an increased risk of HIV transmission compared with exclusive bottlefeeding.[273] Complete avoidance of breast-feeding is recommended in resource-rich settings where there is access to safe, affordable, and culturally acceptable alternatives.[246]

HIV-2 INFECTION

Although HIV-1 is associated with the global HIV pandemic, in some areas of the world, HIV-2 is endemic and is an important cause of HIV infection. It is estimated that 1 to 2 million people are infected with HIV-2 globally, with some being concurrently infected with HIV-1.[274] HIV-2 is endemic in West Africa, although its prevalence rate in some West African countries is declining.[275,276] HIV-2 infection is not limited to West Africa as cases have been seen around the world, for example, Southern Africa, North and South America, Europe, the Middle East, and Asia–Oceana. Concurrent infection with HIV-1 and HIV-2 can occur in areas where both viruses circulate, although it is most common in West Africa where approximately 5 to 10% of HIV-infected persons are thought to have both viruses.[276]

HIV-1 and HIV-2 share similar routes of transmission, although transmission of HIV-2 does not seem to be as efficient as with HIV-1, particularly with regards to perinatal transmission.[277,278] Patients infected with HIV-2 tend to have lower levels of viremia than with HIV-1 and there is less viral shedding in the genital tract.[279] HIV-2 seems to be less pathogenic than HIV-1 and have a longer asymptomatic stage, a slower decline in CD4 counts, and as mentioned before, there are lower levels of plasma viremia in chronically infected patients.[280,281] Data is conflicting if dual infection with HIV-1 and HIV-2 incurs a different course than the natural history of HIV-1.[282,283]

Treatment of HIV-2–infected patients is complicated by the fact that there are no clinical trial data and the use of VL and drug resistance assays for HIV-2 are not commercially available. It is also not known if the viral suppression of HIV-2 with treatment helps to decrease transmission. The CD4 count is the primary indicator for immune function in both HIV-1 and HIV-2–infected patients, and although it may take longer for HIV-2–infected patients to have a decline in CD4 counts, once it is less than 200 cells/mm^3, there is an increased risk for mortality and morbidity related to OIs.[280,281,284]

The regimen(s) used to treat HIV-1 and HIV-2 is different. In general, HIV-1 and HIV-2 are equally susceptible to NRTIs but there is variable activity against HIV-2 with PI agents.[285,286] Limited data suggests that some integrase inhibitors work well against HIV-2 and that CCR5 coreceptor antagonists may also be effective.[287,288] HIV-2 is intrinsically resistant to NNRTIs, including second-generation drugs and to enfuvirtide, a fusion inhibitor.[68,289,290] There is no data on the optimal time to start ART in HIV-2 infections but recommendations include its use for all symptomatic patients (regardless of CD4 count), patients with comorbidities that would benefit from ART, and various countries use CD4 counts ranging from 300 to 350 cells/mm^3.[290–292] As noted earlier, there are no clinical trials evaluating the selection of ART medications for HIV-2 infection. Two NRTIs should form the backbone of therapy but the third drug should not be an NNRTI due to intrinsic resistance. One possible regimen to start with is tenofovir plus either emtricitabine or lamivudine or zidovudine plus lamivudine *and* ritonavir-boosted lopinavir. HIV RNA testing is limited for HIV-2 but it is recommended at baseline and then shortly after starting ART, followed by testing two to four times per year. CD4 counts should be followed as well and a decline may indicate virologic failure and risk of disease progression. The guidelines for preventing OIs in HIV-2–infected patients are the same as those for patients with HIV-1 infection.

CLINICAL NOTES

- HIV-infected women tend to be diagnosed later in the disease process than men and often have poorer access to HIV specialists and medications.
- Estimates are that at the end of 2011, there were 16.6 million women living with HIV/AIDS globally.
- At the end of 2011, 21% of new HIV infections in the United States were in females, with almost 90% of infections occurring through heterosexual contact.
- In 2010 in the United States, rate of new HIV infections among Black women was 20 times that of White women and nearly 5 times that of Hispanic women.
- Opt-out screening is now recommended as a component of routine management in all health care settings in the United States.
- HIV screening should be a routine part of preconception care.
- Testing based on risk factors alone has failed to identify a large number of people with HIV infection.
- Antibodies to gp41 (envelope protein) and p24 antigens are the first detectable serologic markers following HIV infection.
- WB is the most widely accepted confirmatory assay for diagnosing HIV infection.
- Patients with IWB results should be retested within 1 to 3 months based on the clinicians' assessment of risk factors and counseled to avoid activities that could transmit the virus until repeat testing is performed.
- Viral detection of HIV, either by DNA or quantitative RNA should not be used alone for diagnosis and are not considered screening tests for HIV.
- A positive screening rapid test result requires confirmation with a supplemental test such as a WB.
- Acute and early HIV infection may result in the acute retroviral syndrome, but for 10 to 60% of patients, the early stages of infection are asymptomatic.
- The diagnosis of acute HIV infection is established by the detection of HIV viremia, either through a viral RNA or p24 antigen test, in the setting of a negative or indeterminate HIV serologic test pattern in a patient with clinical features suggestive of the acute retroviral syndrome.
- The average life expectancy for an HIV-infected patient in the absence of treatment is approximately 10 to 12 years.
- The CD4 count and plasma VL are two important and independent laboratory determinants of the rate of progression of HIV infection. Of the two, the CD4 cell count is the strongest predictor of disease progression and survival.
- Even with a low VL, the risk of HIV transmission exists so a form of barrier contraception is always recommended.
- Any patient with a CD4 count less than 200 cells/mm^3 should be assessed for primary OI prophylaxis according to guidelines.
- Approximately 30% of HIV-infected patients in the United States are coinfected with hepatitis C virus (HCV), and about 8% are coinfected with hepatitis B virus (HBV).
- All patients with early HIV infection should undergo drug resistance testing, regardless of whether treatment is going to be started or not.
- An ART regimen is described as having a backbone and a base. The backbone typically consists of two NRTIs. The base has traditionally included either an NNRTI or a PI, although a drug from the integrase inhibitor class is also a possible base option.
- Regimens with three different classes of drugs are no more potent than regimens made up of two different classes of drugs.
- Ritonavir is used to "boost" the serum concentration of other PIs.
- The management of ART is complex and should be delivered by providers with specific training.
- General intolerance to ART agents appears to be more common in women than men and leads to increased discontinuation rates.
- The FDA has categorized efavirenz as category D, but it can be used after the first trimester in select cases.
- Transmission of HIV from male to female is more common and more efficient compared to female-to-male transmission.
- Male condom effectiveness in preventing HIV transmission is approximately 80%, but when used consistently, their effectiveness can be as high as 95%.
- STI increases the transmission of HIV by increasing the viral burden in the genital tract and by increasing susceptibility to HIV.
- The per-contact risk of transmission from sexual exposure varies according to the nature of exposure.
- Optimally, a course of nonoccupational PEP should begin as soon as possible after exposure and within 72 hours of exposure.
- Follow-up testing after baseline testing due to HIV exposure should be done at 4 to 6 weeks, 12 weeks, and 6 months after the exposure.
- Among HIV-infected women using IUDs, there is no increased risk of overall complications or infectious complications.

(continues)

- Oral hormonal contraceptive use may increase the risk of HIV transmission by its association with cervical ectopy and thereby HIV shedding or by its effect on lowering the vaginal pH.
- Antiretroviral drugs can interact and potentially increase or decrease the bioavailability of hormonal contraceptives.
- Recommendations for cervical screening in HIV-infected women are different from those for HIV-uninfected women.
- Women with HIV have an increased incidence for VIN.
- BV is more prevalent and more persistent among HIV-infected women.
- ***T. vaginalis*** has been shown to increase the risk of HIV acquisition.
- Cervicitis plays an important role in the transmission of HIV, both by increasing susceptibility to HIV infection and increasing HIV viral shedding.
- The most common causes of GUD among HIV-infected women are HSV and syphilis, although often no etiology is identified.
- All HIV-infected women and discordant couples should undergo discussion and counseling regarding options for parenthood and reproduction.[204] Preconception counseling should include discussion regarding effective contraception to reduce the likehood of unintended pregnancy.
- The risk of perinatal transmission, in the absence of intervention is approximately 25%. In developed countries, interventions have reduced the rate of vertical transmission less than 2%.
- Antiretroviral prophylaxis is recommended for all pregnant women.
- Intrapartum intravenous ZDV is recommended for all HIV-infected women, unless contraindicated due to hypersensitivity. The recommended dose is 2 mg/kg loading dose administered over 1 hour followed by 1 mg/kg/hour until delivery.
- The American College of Obstetricians and Gynecologists recommends that women with detectable virus levels greater than 1000 HIV RNA copies/mL should undergo scheduled cesarean section.
- Insufficient data exist regarding women with VLs that are detectable but less than 1000 copies/mL, and management decisions should be made on an individual basis.
- Although HIV-1 is associated with the global HIV pandemic, in some areas of the world, HIV-2 is endemic and is an important cause of HIV infection.
- HIV-2 seems to be less pathogenic than HIV-1 and have a longer asymptomatic stage, a slower decline in CD4 counts, and there are lower levels of plasma viremia.
- The regimen(s) used to treat HIV-1 and HIV-2 are different.
- Clinicians in the United States may seek expert telephone advice through the National HIV/AIDS Clinician's Consultation Center, 24 hours a day (1-888-448-4911).

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SECTION IV

Office Procedures

CHAPTER 28

Office-Based Procedures

Silvia T. Linares and Jenny J. Duret

Office-based procedures have been an integral part of the gynecologic practice. Colposcopy, cervical and vaginal biopsies, and intrauterine devices insertion are done in the office since their inception more than 50 years ago. The increment in office procedures probably corresponds to better reimbursements, greater satisfaction for patients and physicians, and a safe and efficient way to provide a service.[1] Patients have better scheduling options, a known environment within the office, and can avoid the hassle of going to a hospital or a surgery center to have a procedure done. For doctors and their staff, the advantages are clear: control of costs and sense of doing something innovative with better time management.[1,2,4] In 2013, the Joint Commission established the national patient safety goals for the ambulatory health care accreditation program. Some of those goals are very relevant to the implementation of an office-based procedure program. For example[2,3]:

1. Goal 1 improves the accuracy of patient identification. (Use at least two patient identifiers.)
2. Goal 2 improves the safety of medication use. (Label all medications, medications containers, and other solutions on and off the sterile field in perioperative and other procedural settings; maintain and communicate accurate patient medication information.)
3. Goal 7 reduces the risk of health care–associated infections (hand hygiene guidelines from the Centers for Disease Control and Prevention [CDC] or the World Health Organization [WHO].)
4. The introduction of the universal protocol for preventing wrong site, wrong procedure, specifically:
   - Conduct a preprocedure verification process. In gynecology, a written diagram can be used with the patient because it is anatomically impossible or impractical to mark the site.
   - A time out is performed before the procedure.[3]

OFFICE SET UP

Make sure that the room assigned is in compliance with the fire, occupational safety, and health administration codes; has all the necessary equipment to supply the level of anesthesia needed or chosen instruments such as a pulse oximeter, blood pressure and pulse heart rate monitors, reliable oxygen source, resuscitation equipment including defibrillator, cardiac monitor, auxiliary electrical power source; and that the equipment used for the procedures has been serviced, tested, and inspected.[2,5–7]

With the increase in office-based procedures, it is imperative to have a safe practice. It is preferable to have a special room and identified staff dedicated to the offered procedures. Depending on the type of practice (solo vs. group), a responsible practitioner needs to ensure the creation of protocols, checklists, and policies within the practice that will assure the success of more invasive and technological difficult procedures.[5]

PAIN MANAGEMENT FOR OFFICE PROCEDURES

Pain management is the most challenging component of a successful office procedures program. Have in mind that patient selection and experience will probably overcome this obstacle. There are different levels of anesthesia (pain control)[6,8,9]:

Level 1: local anesthesia with minimal or no preoperative oral anxiolytic medication
Level 2: moderate sedation
Level 3: deep sedation or general anesthesia

Level 1 (local anesthesia with minimal or no sedation) is the recommended level for the majority of the office procedures described in this chapter, but have in mind

that level 2 is an option in the office setting if you can have an anesthesiologist present during the procedure or there is a non-anesthesiologist with training to provide deep sedation or general anesthesia in your practice.[8,9]

Paracervical Block

Paracervical block has been described in the literature since the beginning of the last century.[10] It was used to provide pain control in early labor[11] and is actually the procedure of choice for gynecologic office procedures.[12] Innervation of the uterus and cervix arise from the S2–S4 roots and nerves travel to the uterus in the lower portion of the broad ligament to the paracervical ganglion. Anesthesia of this plexus is the basis of the paracervical block.[11,13] Paracervical block is used for LEEPs, diagnostic and operative hysteroscopy (tubal occlusion and global endometrial ablation), pregnancy terminations, some difficult endometrial ablations, IUD insertions, and cervical biopsies.[12–14]

Contraindications are allergy to anesthetic agent and local infection. The technique of paracervical block itself is not standardized. Several studies have demonstrated that paracervical block diminished pain perception in patients going under in-office gynecologic procedures. There are multiple reports describing where the local anesthetic should be injected, for example, at 4 and 8 o'clock,[15] 3 and 9 o'clock, 3-5-7-9 o'clock,[16] and injecting the anesthetic at the cervicovaginal junction or in the cervical stroma.[13] Beneficial techniques include use of carbonated lidocaine, deep injection to 3 cm, a four-site injection, slow injection (over 60 seconds), and waiting 3 to 5 minutes before the schedule procedure.[14,17,18]

Equipment[12,17,18]

1. 22-gauge, 1.5-in needle × 1 (to inject), 18-gauge needle × 2 (to draw)
2. Needle extender × 1
3. 10 mL syringe × 1, 20 mL control syringe (Luer lock type) × 1
4. Single-tooth tenaculum
5. Lidocaine (1%) 20 mL
6. Ropivacaine (0.2%) 30 mL
7. 2 mL 8.4% sodium bicarbonate
8. Sterile Q tip (6, large)
9. Sterile cup (to mix anesthetics)
10. Antiseptic (povidone-iodine or chlorhexidine)
11. Speculum

Procedure

1. Mix 30 mL ropivacaine, 10 mL lidocaine, and 10 mL normal saline in a sterile cup and 2 mL 8.4% sodium bicarbonate.
2. Use 20 mL control syringe and an 180-gauge needle to draw the anesthetics; change to 22-gauge, 1.5-in needle on a needle extender.
3. Insert the speculum, examine the cervix, and use a large Q-tip and antiseptic to clean the cervix and the fornices.
4. Inject 1 mL of the preparation or 1% lidocaine at 12 o'clock position of the cervix, at the tenaculum site.
5. Apply single-tooth tenaculum.
6. Inject 7.5 to 10 mL of the preparation at 3-5-7-9 o'clock or 4 and 8 o'clock.
7. Wait 3 to 5 minutes for the preparation to work.

Complications

- Local anesthetic toxicity and intravascular injection that can produce convulsions, cardiac arrhythmias, and respiratory arrest. After the injection, ask patient about metallic taste because it is an early sign of systemic toxicity.[19]
- Vasovagal reaction with rapid onset of bradycardia, hypotension, pallor, and faintness
- Anaphylaxis signs are hypotension, bronchospasm, urticaria, and edema.[20]

All complications can be fatal and the provider needs to have advanced cardiac life support (ACLS) training and all the necessary equipment to manage the complications and a plan in place to transfer patients to a nearby hospital.

BARTHOLIN DUCT CYST AND ABSCESS

Bartholin gland cysts and abscesses account for 2% of gynecologic visits per year[21] and result from an obstruction of the Bartholin duct, which is followed by the accumulation of mucus within the duct. This fluid may become infected and become purulent, therefore constituting an abscess. The Bartholin cysts are commonly asymptomatic, but patients with larger cyst may complain of discomfort during intercourse or pain while sitting or walking. Patients with Bartholin abscesses, however, tend to complain of pain and a rapidly enlarging unilateral vulvar mass,[22] and on exam, erythema of the skin overlying the abscess may be present, as well as fever, tachycardia, cellulitis, and an elevated white blood cell (WBC) count. These abscesses are usually fluctuant masses located on the right or left of the introitus, external to the hymenal ring and at the lower aspect of the vulva near the posterior fourchette (at 5 and 7 o'clock). Once drained, the purulent fluid from the abscess may be sent for culture and usually reveals a polymicrobial infection. The bacteria commonly found are *Bacteroides* species, *Peptostreptococcus* species, *Escherichia coli,* and *Neisseria gonorrhea*.[23] Incision and drainage (I&D) alone may give immediate relief but probably temporary. Unless a new tract is created, the incision edges may seal and cause a re-accumulation of mucus or pus.

Permanent resolution usually occurs following an I&D with Word catheter placement and marsupialization, which are the two main outpatient managements

used and discussed in this chapter. Silver nitrate gland ablation and carbon dioxide laser treatments have also been used. The silver nitrate treatment has only been documented in Turkey and has been associated with vulvar mucosal cauterization,[22] but when compared to marsupialization revealed complete healing with less scar formation.[24] Both silver nitrate ablation and carbon dioxide laser treatments need further data before they can be accepted as standard treatment methods[25] (Figs. 28.1 and 28.2).

Incision and Drainage With Word Catheter Placement

Indication

Small asymptomatic cysts should be left alone. In symptomatic Bartholin cyst or any Bartholin abscess, an I&D followed by Word catheter placement is an option for management and provides in most cases immediate relief to the patient. The Word catheter is made of latex with an inflatable balloon at one end and an injection hub at the other end. The principle behind this procedure is to create a fistula by placing the catheter into the cyst to form a permanent epithelialized tract.[21] The procedure can be performed under local anesthesia. The Word catheter has its limitations however, such as difficulty of maintaining the catheter in the correct place for the appropriate interval time of 4 to 6 weeks.

Contraindications

There are no absolute contraindications to performing an I&D and Word catheter placement.

Equipment

- 1% lidocaine with syringe to inject it
- Scalpel (no. 11 blade) and handle

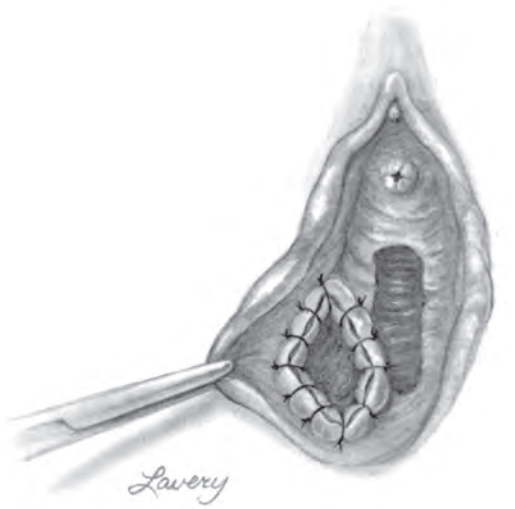


FIGURE 28.1 Vulvar disease, Bartholin gland cyst. (Courtesy of LifeART image copyright © 2014 Lippincott Williams & Wilkins. All rights reserved.)

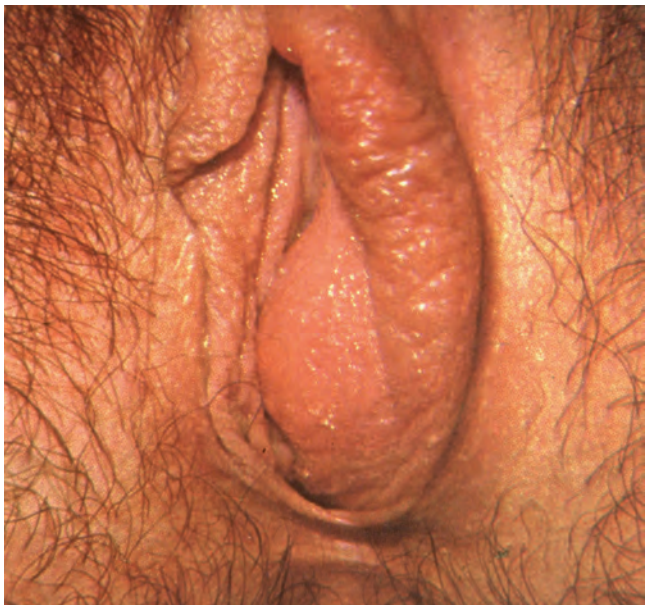


FIGURE 28.2 Bartholin gland cyst. (Image from Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.)

- Betadine (or another antiseptic solution)
- Hemostat
- Culture swab
- Word catheter (Fig. 28.3)
- Syringe with 2 to 3 mL of sterile saline

Procedure

1. Place the patient in the dorsal lithotomy position.
2. Cleanse the area of the Bartholin cyst/abscess with a suitable antiseptic solution.
3. Inject 1% lidocaine at the expected incision site.
4. With the scalpel, make a 1 cm incision, which should be on the medial side of the cyst, close and parallel to the hymenal ring. The thinnest area is desired.
5. Send culture of the drained fluid.
6. A hemostat may be used to break any loculations.
7. Biopsy of the cyst wall may be indicated in women older than 40 years of age.
8. Diluted Betadine placed into a syringe can be used to irrigate the cyst cavity.

FIGURE 28.3 Word catheter.

9. A Word catheter is then placed into the cyst cavity to keep the drainage tract open. The tip of the deflated Word catheter is placed into the cyst cavity and the balloon is then inflated by injecting 2 to 3 mL of sterile saline into the port of the catheter.
10. Finally, tuck the hub of the catheter into the vagina to prevent dislodgement.

Aftercare

If the procedure was performed for an abscess, significant cellulitis may be present, warranting an antibiotic regimen. The antibiotic should be broad spectrum to cover polymicrobial infections (anaerobes and aerobes).[21] Patients should be instructed to perform sitz baths twice daily. Ideally, the catheter is to remain in place for 4 to 6 weeks, although it often falls before this time. There is no need to try to replace the catheter if dislodged early; it is usually impossible to do due to a decrease in cavity size. If the catheter remains in place for 3 to 4 weeks, the tract becomes epithelialized and the catheter can be removed.

Complications

Patients should be counseled about the risks of bleeding, pain, and repeat infection. A recurrence of the Bartholin cyst or abscess is common following an I&D alone or with early dislodgement of the Word catheter. The recurrence rate is 2 to 17%. Patients should be aware of the possible need for a repeat I&D or a marsupialization.

Marsupialization

Indications

Recurrences of Bartholin cysts or abscesses are common after a simple I&D. In these cases, a marsupialization is an option. Since the use of the Word catheter, however, the marsupialization procedure has had limited use. Their recurrence rates are similar and the marsupialization procedure requires a larger incision, placement of sutures, and longer procedure time compared to the I&D and Word catheter placement.[24] The procedure entails creating a new duct to prevent a re-accumulation of mucus or pus.

Recurrence rates after a marsupialization is low and it makes it possible to avoid excising the gland with the cyst, allowing preservation of the secretory function of the gland for lubrication. The excision of the gland, a bartholinectomy, has been associated with many complications, including failure to remove the entire cyst, intraoperative or postoperative hemorrhage or hematoma, and occasionally, formation of scarring tissue. The marsupialization can be performed in the office (under local anesthesia or a pudendal block) or in the operating room (under general or regional anesthesia).

Contraindications

Marsupialization of a Bartholin abscess is contraindicated. In general, definitive surgical management is best deferred until a period of quiescence.

Equipment

- 1% lidocaine with syringe to inject it
- Scalpel
- Alice clamps
- Hemostat
- Delayed absorbable suture
- Needle holder
- Suture scissors

Procedure

The patient should be placed in the dorsal lithotomy position and the vagina and the vulva should be sterilely prepped.

1. A 2- to 3-cm skin incision parallel to the hymenal ring is performed using the scalpel. Care should be taken to only incise the skin and not puncture the cyst wall. The fluid-filled cyst should be visualized at this time.
2. The cyst wall is then incised with the scalpel, and the incision is extended superiorly and inferiorly. Allis clamps are then placed at the superior, inferior, right, and left edges of the cyst.
3. Using the tip of a hemostat, break any loculations that may be present in the cyst cavity.
4. Biopsy of the cyst wall may be indicated in women older than 40 years of age.
5. The cavity should be rinsed with normal saline.
6. The edges of the cyst wall are then sutured to the vestibule with interrupted sutures using 2-0 or 3-0 delayed absorbable suture.

Aftercare

Warm sitz baths once or twice daily are recommended to aid in pain relief and wound cleansing. Patients should be seen within a week after the procedure to confirm that the new duct is still patent. Within 2 to 3 weeks, the ostium shrinks to a 5 mm or less opening.

Complications

Recurrences after marsupialization are rare. However, if a recurrence occurs, a marsupialization may be repeated or a bartholinectomy may be warranted.

INTRAUTERINE DEVICE PLACEMENT AND REMOVAL

There was a time when approximately 7% of sexually active women in the United States used an intrauterine device (IUD) for contraception. However, the popularity

of the IUDs has fallen. In 1995, the National Survey of Family Growth reported that fewer than 1% of women who use contraception use an IUD.[28] The IUDs are more common in China where 40% of women use them for contraception.[28] The two devices approved for use in the United States are the Mirena (levonorgestrel-containing device) and the Paraguard T 380A (copper-containing). The respective failure rates for these devices are 0.1 and 0.8%, respectively.[29] The Mirena releases levonorgestrel at a constant rate of 20 mcg/day. The Paraguard is wound with fine copper wire for a total of 380 mm^2 of copper.[30]

Indications

IUDs are effective reversible contraceptive methods, made of nonabsorbable material (most often polyethylene), that do not have to be replaced for 5 (Mirena) and 10 years (copper T). The Mirena can also be used as management for menorrhagia by reducing menstrual blood flow, which in turn is often associated with reduction in dysmenorrhea.[31,32] Even though there is a higher up-front cost, their long-term cost effectiveness is competitive with other forms of contraception.[30]

Contraindications

General contraindications to IUD placement are pregnancy, uterine abnormalities causing distortion of the endometrial cavity, acute cervicitis or pelvic inflammatory disease, postpartum endometritis or infected abortion in the past 3 months, abnormal uterine bleeding of unknown etiology, women with multiple sexual partners, and a history of a prior ectopic pregnancy.[28,30]

The Paraguard is also contraindicated in patients with a copper allergy or history of Wilson disease. The Mirena is contraindicated in women with known or suspected carcinoma of the breast, hypersensitivity to any component of the device, or with acute liver disease or tumor.[33]

Equipment

Practitioners should have this list of equipment for placement of an IUD:

1. Sterile gloves
2. Speculum
3. Betadine solution (or another antiseptic solution)
4. Single-tooth tenaculum
5. Uterine sound
6. IUD package
7. Scissors

Procedure

Once the practitioner rules out any contraindications to placement, the patient should be counseled about all the risks and benefits associated with the device. Patient should sign an informed consent before the procedure.

Paraguard Placement (Figs. 28.4 and 28.5)

1. Place the patient in the dorsal lithotomy position.
2. Perform a bimanual exam to note the size and position of the uterus and assess for any adnexal masses.

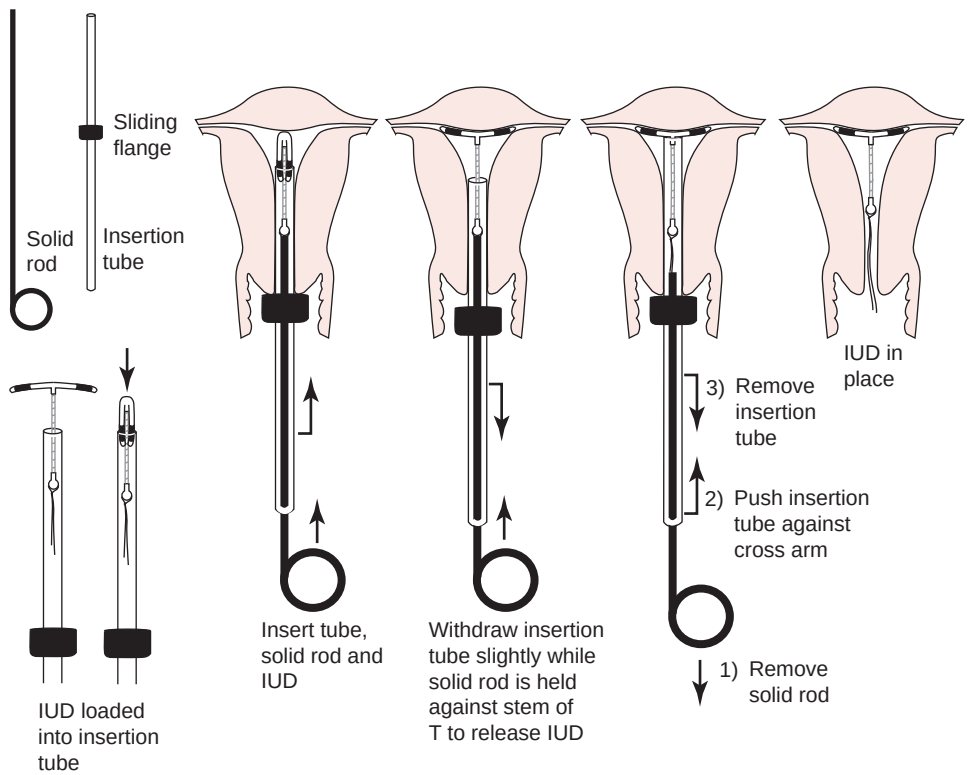


FIGURE 28.4 ParaGard insertion. (From Beckmann CRB, Frank W, Smith RP, et al. *Obstetrics and Gynecology*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.)

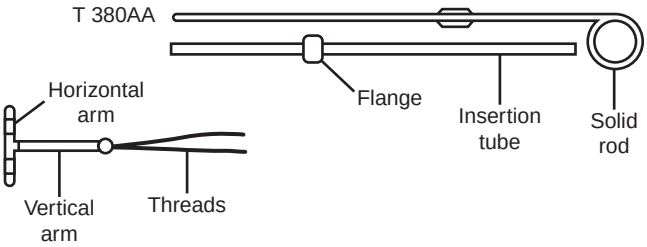


FIGURE 28.5 ParaGard IUD from ParaGard insert.

If any abnormalities are found, they should be evaluated prior to placement of the device.

3. Place a speculum in the vagina, allowing visualization of the cervix.
4. Cleanse the cervix with an antiseptic solution, such as Betadine.
5. Using sterile technique, place the single-tooth tenaculum at the anterior lip of the cervix.
6. Sound the uterus and then place the blue plastic flange on the outside of the inserter tube at the sounded distance from the tip of the device.
7. Load the device into the inserted tube and tuck the arms into the tip of the inserter.
8. While stabilizing the cervix and straightening the cervical canal with the tenaculum, the inserter tube, with the device loaded, is then passed through the external os into the endometrial cavity until the blue flange abuts the cervix.
9. Hold the solid white rod in the tube steady, and then withdraw the inserter tube no more than 1 cm to allow release of the arms into the cavity.
10. Move the insertion tube upward toward the fundus until resistance is felt to ensure placement of the device at the highest position in the uterus.
11. Withdraw the solid white rod and the insertion tube. Only the strings should be visible protruding through the cervix.
12. Cut the strings so that 2 to 3 cm of thread protrude into the vagina.
13. Remove the tenaculum and assure hemostasis at the tenaculum puncture sites. Hold pressure if needed.

Mirena Placement (Figs. 28.6 and 28.7)

The Mirena placement is slightly different from the Paraguard.

1. Pick up the Mirena from the package and release the strings from behind the slider.
2. The slider should be positioned at the top of the handle, end closest to the device.
3. Align the arms of the device horizontally and pull on the threads to draw the device into the insertion tube.
4. Set the flange at the distance measured by the sound.
5. With the tenaculum placed at the anterior lip of the cervix, apply some traction on the cervix and insert

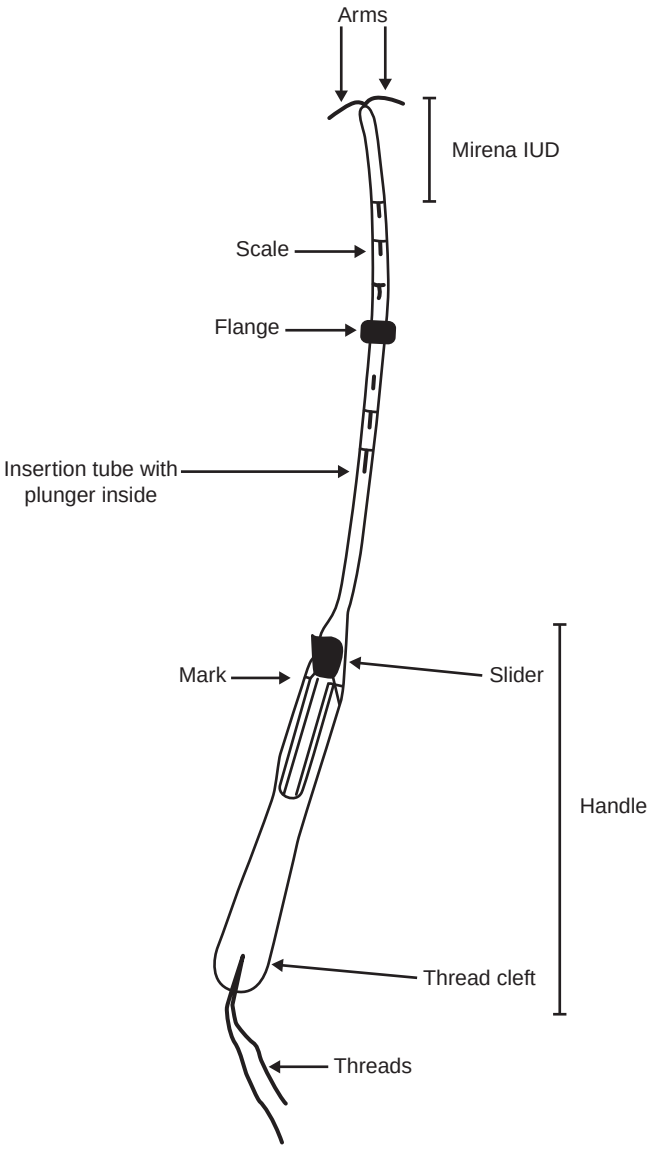


FIGURE 28.6 Mirena IUD from Mirena insert.

the tube into the endometrial cavity until the flange is ~1.5 cm away from the external os.

6. While holding the insertion tube steady, release the arms by pulling the slider back until the top of the slider reaches the raised horizontal mark on the handle.
7. Push the inserter forward until the flange touches the cervix, which should bring the device to the fundus.
8. Release the device by pulling the slider down all the way. This will release the threads.
9. Remove the inserter from the uterus and cut the threads so that they protrude 2 to 3 cm for the external os.

Aftercare

Patients should be allowed to feel the consistency of the threads after placement of the device and counseled to check for the strings every month after their menses to

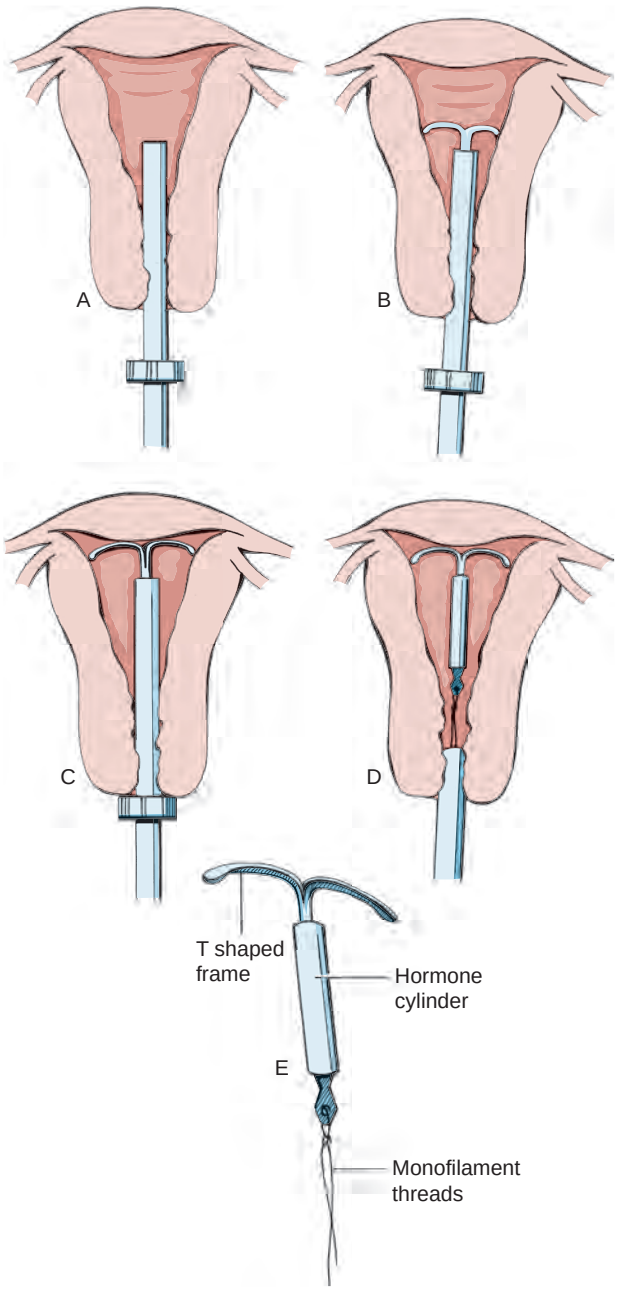


FIGURE 28.7 The Mirena intrauterine device. **A:** Insertion of Mirena into uterine cavity. **B:** The arms of the Mirena are released. **C:** Mirena is positioned near the uterine fundus. **D:** Releasing the Mirena IUD and withdrawing the inserter. **E:** The Mirena IUD. (From Gibbs R, Karlan B, Haney A, et al. *Danforth's Obstetrics and Gynecology*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2003.)

confirm the device is still in place. Patients should also return to their practitioner to confirm visualization of the strings 1 month after placement.

Complications

Numerous complications from these devices have been described. However, they are usually not serious and the serious complications are not common.[28,30,34]

Expulsion

The expulsion of the device is most common in the first month after placement. Patients should be taught how to palpate for the strings. Patient should be examined 1 month after placement to confirm appropriate placement by visualizing the strings.

Uterine Perforation

A uterine perforation may be silent or clinically apparent. It is a complication that can occur early in the placement of the devices, while sounding the uterus or during insertion. Its occurrence rate is approximately 1 per 1000 insertions.[35] The devices may also migrate through the uterine wall and can be partially or completely in the abdominal cavity.[35]

Loss of Device

When the strings of the device cannot be visualized protruding through the external os, the device may have been expelled or may have migrated in the uterus or perforated the uterus into the peritoneal cavity. Gentle probing with a hook may be performed because in some instances the strings could be in the cervical canal in a well-positioned IUD. If the device is not felt with gentle probing, sonography to evaluate the uterine cavity should be performed.[36] If the device is in the uterus and removal is needed or desired, it can be performed hysteroscopically. If the device is not visualized in the uterine cavity, a plain x-ray of the abdomen and pelvis is warranted.[36] Laparoscopic removal of the device can be performed once identified in the abdominal cavity[37] (Fig. 28.8).

Cramping and Bleeding

Patients should be counseled that uterine cramps and bleeding soon after the insertion of the IUD is common and may persist for a variable time. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be administered to decrease the cramping. Irregular menses for a period of time can also be experienced, especially with the Mirena.

Menorrhagia

The Copper IUD has been associated with increased blood loss, in approximately 11% of women.[38,39] The Mirena, in contrast, is associated with a progressive amenorrhea (usually after a period of irregular bleeding), reported in 20% of women at 5 to 6.5 years of use and 60% at 7 to 12 years of use.[40]

Infection

The major risk of infection is at the time of insertion and does not increase with long-term use.[28,34] The main risk factors for an infection are sexual behavior and history

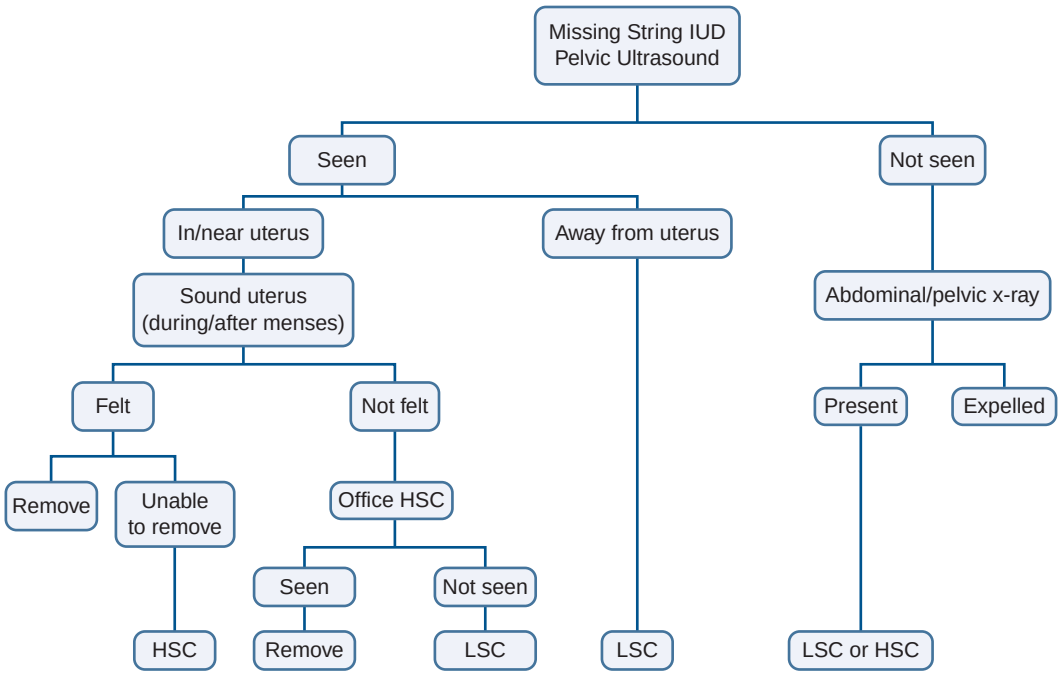


FIGURE 28.8 Algorithm for managing the "missing string" IUD. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. Philadelphia: Lippincott Williams & Wilkins; 2007.)

of sexually transmitted diseases. Therefore, appropriate counseling and patient selection are key. With suspected pelvic infection, however, there is mixed evidence of whether the IUD should be removed after therapy has been initiated.[41]

Pregnancy With Retained Intrauterine Device

Early location of the pregnancy is important in women with a known IUD in situ, to rule out an ectopic pregnancy. With a positive pregnancy test, if the strings are visualized protruding from the cervical os, the IUD should be removed. The incidence of spontaneous abortion more than doubled when the IUD remained in utero. The chance of a live birth being premature was four times greater when the IUD remained in situ than when it was removed.[42] If the tail is not visible, sonography may be used to attempt to locate the device. Patients should be counseled that they are at risk for early pregnancy loss, low birth weight from preterm delivery, and intrauterine infection.[43]

Ectopic Pregnancy

Most intrauterine pregnancies are prevented with the IUDs. However, if pregnancy were to occur, there is a higher risk of an ectopic one.[30]

Removal of Intrauterine Device

The removal of the IUDs is simple. Place a speculum into the vagina, allowing visualization of the cervix and the strings protruding from the external os. Grasp the strings with ring forceps and pull steadily until the device exits the os.

ENDOMETRIAL BIOPSY

An endometrial biopsy is an office procedure during which a tissue sample is taken from the lining of the uterus. In the past, dilation and curettage was the method of choice for diagnosing endometrial pathology in women with abnormal uterine bleeding. However, an in-office endometrial biopsy is a minimally invasive technique, believed to reduce the cost of the abnormal uterine bleeding workup without reducing accuracy.[44] There are different instruments in use to perform the endometrial biopsy: The Novak curette is a thin metallic tube with a side opening at the tip. Suction with an attached syringe can be applied to help remove the endometrial tissue. The Pipelle is a more flexible plastic tube with a side opening at the tip. Recently, the TruTest has been introduced as an alternative method of endometrial biopsy. Rather than using a suction tube, this method uses the Tao Brush to gently brush the lining of the uterus.[45] The indications and contraindications to performing an endometrial biopsy are listed in Table 28.1.

Equipment

Prior to performing an endometrial biopsy, the following equipment should be available:

- Sterile gloves
- Vaginal speculum
- Antiseptic solution (such as Betadine)

TABLE 28.1 Indications and Contraindications to Performing an Endometrial Biopsy

Indications	Contraindications
• Abnormal uterine bleeding • Postmenopausal bleeding • Amenorrhea for 1 year or longer • Endometrial dating (define phase of menstrual cycle) • Evaluation for infertility • Atypical glandular cells on Pap smear • Follow-up for previously diagnosed endometrial hyperplasia and/or atypia	• Pregnancy • Acute cervicitis or pelvic inflammatory disease • Clotting disorders • Cervical cancer

- Single-tooth tenaculum
- Pipelle endometrial suction catheter
- Formalin containing specimen cup
- Uterine sound if Pipelle without measuring scale
- Cervical dilators (leave unopened; usually not needed)

Procedure

Patients should be counseled about risks and benefits of the procedure and a verbal or written consent should be obtained prior to performing the procedure. Patients should be advised that cramping during and after the procedure is to be expected and NSAIDs can be given prior to and after the procedure.[45] Once all contraindications have been ruled out, you may proceed with the procedure:

1. Perform a bimanual exam to assess the uterine size and position.
2. Insert a speculum into the vagina allowing visualization of the cervix.
3. If a Pap smear or other cervical procedure is indicated, do so prior to the endometrial biopsy.
4. Cleanse the cervix with the antiseptic solution (Betadine or chlorhexidine).
5. Grasp the anterior lip of the cervix with the single-tooth tenaculum to straighten the uterocervical junction.
6. Insert the Pipelle into the uterine cavity until resistance at the fundus is felt. Note the sound of the cavity.
7. Withdraw the inner piston of the Pipelle to create suction.
8. Move the Pipelle in and out and rotate the Pipelle 360 degree to the four quadrants of the endometrium.
9. Once the sheath is filled with tissue, express the contents into the formalin-filled container.
10. If more tissue is needed, you may repeat the procedure as long as the Pipelle is not contaminated. Keep the Pipelle from coming in contact with the formalin if planning on repeating the procedure.
11. Remove the tenaculum from the anterior lip of the cervix and ensure hemostasis at the puncture sites.
12. Remove the speculum from the vagina.

If there is difficulty passing the Pipelle into the internal os, small dilators may be used to serially dilate the os, which can be painful to the patient and may warrant the use of a cervical block. Patients can also be brought back after having taken misoprostol a couple of hours prior to the procedure.

Aftercare

Allow the patient to remain supine on the examining table for a couple of minutes after the procedure to avoid any vasovagal reaction. Patient should be counseled about taking an NSAID if pain continues. Patient may resume normal activities, however should not use any tampons or have intercourse for 2 weeks after the procedure. Patients should call the practitioner if any fever, increased pain, bleeding heavier than normal menses, and foul-smelling vaginal discharge is experienced.[46]

Complications

Complications are not common but include uterine perforation, excessive bleeding, pelvic infection, and bacteremia.[46,47]

IN-OFFICE THERAPEUTIC OPTIONS FOR TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

Loop Electrosurgical Excision Procedure (Figs. 28.9 and 28.10)

Also known as electrosurgical loop excision and large loop excision of the transformation zone (LLETZ), it is the most common procedure to treat cervical intraepithelial neoplasia. Loop electrosurgical excision procedure (LEEP) was described in 1989 by Prendiville to remove the entire transformation zone.[48] As the other office procedures discussed in this chapter, it is safe, easy to use, well tolerated by patients, and less expensive than a cold knife cone, with less complications and high success rates ranging from 60 to 90%, depending if the margins are positive or negative.[49]

Indications[50,51]

- High-grade lesion
- Unsatisfactory colposcopy, especially if a high-grade lesion is suspected
- Suspected microinvasion
- Lack of correlation between the cytology and colposcopy/biopsies, especially if a high-grade lesion is suspected

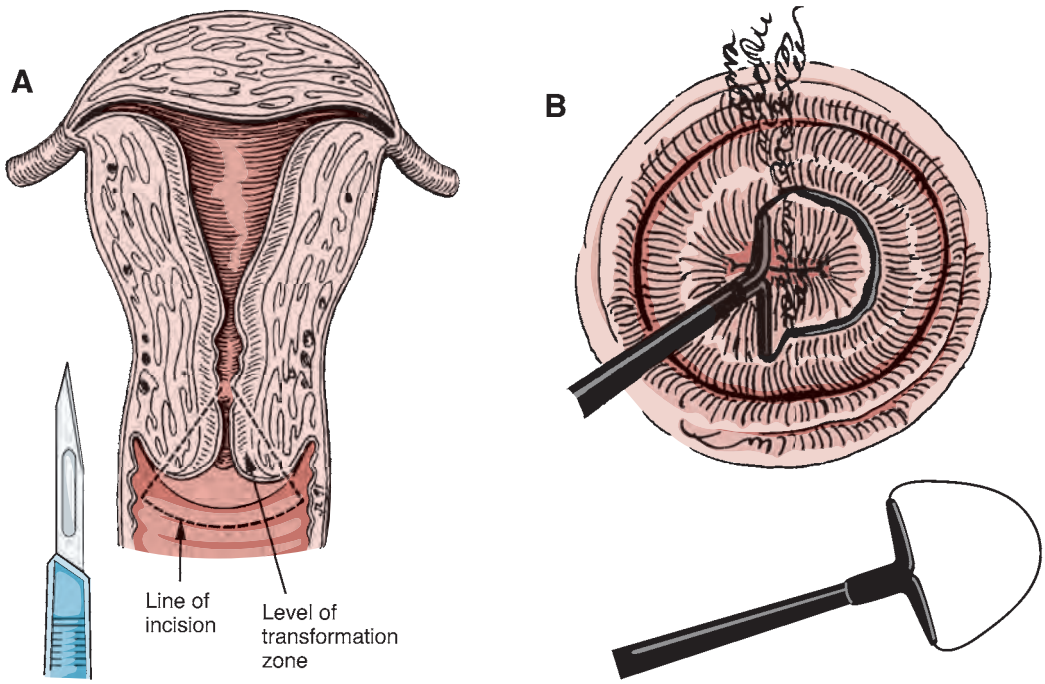


FIGURE 28.9 Conization of the cervix (LEEP vs. cold knife cone). **A:** Cold knife technique. **B:** LLETZ/LEEP (large loop excision of the transformation zone/loop electrosurgical excision procedure) technique. (From Beckmann CRB, Frank W, Smith RP, et al. *Obstetrics and Gynecology*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.)

- Lesion extending into the endocervical canal
- Endocervical curettage showing high-grade lesion or glandular abnormality
- Suspected adenocarcinoma in situ (In this instance, cold-knife conization [CKC] may be preferable because an increased risk of positive margins and higher recurrence risk with LEEP compared to CKC may exist.)
- Colposcopist unable to rule out invasive disease
- Recurrence after an ablative or previous excisional procedure

Contraindications[51]

- Active cervical, vaginal, pelvic infection
- Known frankly invasive cervical cancer
- Use with caution in pregnancy only if there is a strong suspicions of invasive disease
- Use with caution if bleeding disorder exist

Equipment

- Electrosurgical generator
  - High frequency (350 to 1200 kHz)
  - Low voltage (200 to 500 V)
- Grounding pad
- Smoke evacuation system
- Insulated vaginal speculum with smoke evacuation tubing
- Various sizes of LEEP or Fischer cone biopsy excisor electrodes
- 3 to 5 mm ball electrode

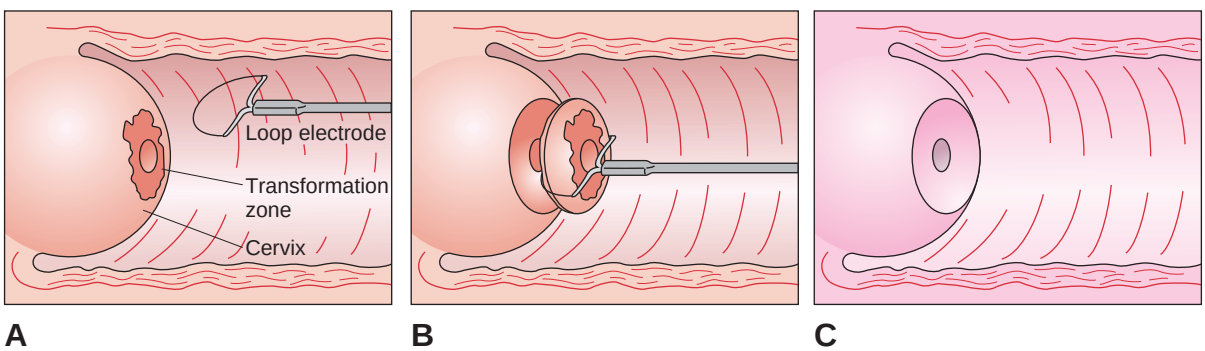


FIGURE 28.10 Loop electrosurgical excision procedure (LEEP) or large loop excision of the transformation zone (LLETZ). **A:** Electrode approach. **B:** Removal of transformation zone. **C:** Excision site (region between endocervix and ectocervix). (From Willis MC, CMA-AC. *Medical Terminology: A Programmed Learning Approach to the Language of Health Care*. Baltimore: Lippincott Williams & Wilkins; 2002.)

- Single-tooth tenaculum
- Monsel solution
- 3 to 5% acetic acid solution
- Aqueous Lugol solution
- Colposcopy
- Cotton swabs
- Vasopressin plus 1% lidocaine solution (10 units in 30 mL of 1% lidocaine) or 1% lidocaine with epinephrine (1:100,000 dilution)
- 25- to 27-gauge needle with 10 mL syringe or dental-type syringe
- Monsel paste or gel
- Specimen bottles with 10% neutral-buffered formalin
- Needle holder
- 2-0 absorbable suture material

Procedure[48]

- Obtain informed consent.
- Place patient in dorsal lithotomy position.
- Insert insulated speculum, with the smoke evacuation tube placed in the vagina.
- Place dispersive pad in the patient's upper thigh.
- Use vaginal side retractor if needed.
- Do a paracervical block.
- Apply acetic acid (3 to 5%) or Lugol solution on the cervix to visualize the entire lesion.
- The electrosurgical generator is set at 30 to 50 watts on blend 1.
- Choose appropriate size loop to make sure the entire lesion will be removed in one pass ideally.
- Control bleeding with a ball electrode and application of Monsel solution to the cone bed.
- Label and identified the specimen.

Complications

- Immediate bleeding if not controlled with cauterization and Monsel. Hemostatic stitches can be used.
- Delayed postprocedure bleeding. If heavy bleeding not related to menses is encountered, the patient will need to be evaluated. Use of Monsel solution, silver nitrate, electrocautery, or packing usually provides adequate hemostasis.[52]
- Infection is very rare (less than 1%). Signs of infection are delayed bleeding and persistent vaginal discharge.[52]
- Cervical stenosis and cervical insufficiency. Cervical stenosis is more common (4.3 to 7.7%) in postmenopausal women, second LEEP, or a very deep LEEP.[52,53,55–57]
- Cervical insufficiency and increased risk of preterm delivery.[54,55]

Aftercare

Patient should be instructed to avoid strenuous activities for at least 2 weeks, pelvic rest for 4 weeks, and nothing per vagina for 4 weeks. A brown discharge can be expected for at least 2 weeks and a follow-up appointment in 6 weeks to review cervical healing and cervical canal patency. Patient will need surveillance in 6 and 12 months with cytology. If positive margins, a repeat cytology with endocervical curettage can be done in a shorter interval.

In conclusion,

- LEEP is a relative simple office procedure performed under local anesthesia.
- LEEP provides tissue for pathologic interpretation.
- The entire transformation zone can be removed in one continuous piece.
- Long-term complications are minimal.
- Patients will need follow-up with cytology to assure resolution of lesion.

HYSTEROSCOPY

Hysteroscopy is the ultimate procedure to evaluate the uterine cavity. The use of hysteroscopy in modern gynecology has expended since its introduction in the early 80s, but there are records of use of hysteroscopy in the 19th century by Pantaleoni.[58]

Diagnostic hysteroscopy is a safe procedure that can be done at the office without or minimal anesthesia.[58] New procedures such as endometrial ablation, tubal occlusion, biopsies, small myomectomies, or polypectomies have moved from for the operating room to the office. Office diagnostic hysteroscopy is based on four pillars: patient selection, instrument quality, characteristics of the distension medium, and the ability and experience of the operators.[58–60]

Indications[58,60,61]

- Menstrual abnormalities
- Infertility evaluation
- Localization of foreign bodies
- Clarify a questionable hysterosalpingogram (HSG) or sonohystogram or a noninvasive radiologic test.
- Evaluate after an endometrial sampling nondiagnostic or without endometrial cells
- Chronic vaginal discharge not attributed to vaginal or cervical disease
- Operative hysteroscopy procedures
  - Endometrial ablation
  - Small myomectomy
  - Polypectomy
  - Lysis of adhesions
  - Removal of IUD
  - Visually directed biopsy
  - *Sterilization* tubal occlusion (Essure)

Hysteroscopic View (Fig. 28.11)

Contraindications

- Pelvic inflammatory disease
- Active herpes infection

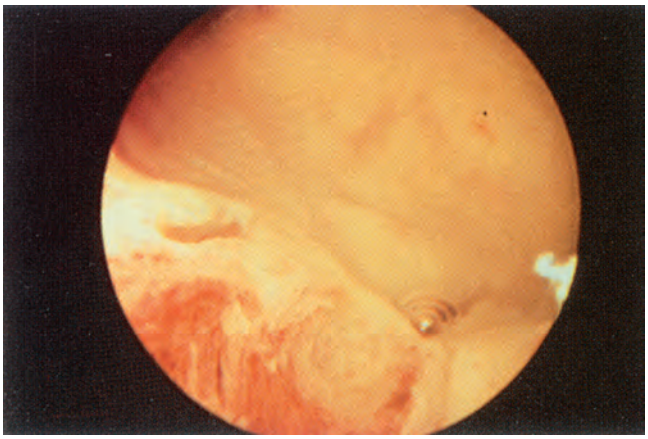


FIGURE 28.11 Hysteroscopic view. Close-up view of a secretory endometrium. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. Philadelphia: Lippincott Williams & Wilkins; 2007.)

- Known intrauterine pregnancy
- Cervical cancer
- Recent uterine perforation
- Severe cervical stenosis
- Unstable patient

Equipment[58–60] (Fig. 28.12)

- Hysteroscope
  - Flexible
    - 1.2 to 4 mm outer diameter
    - 0- to 240-degree visual field (0- to 30-degree angle) (Fig. 28.13)
    - Fiber optic
    - Digital
    - Inflow port

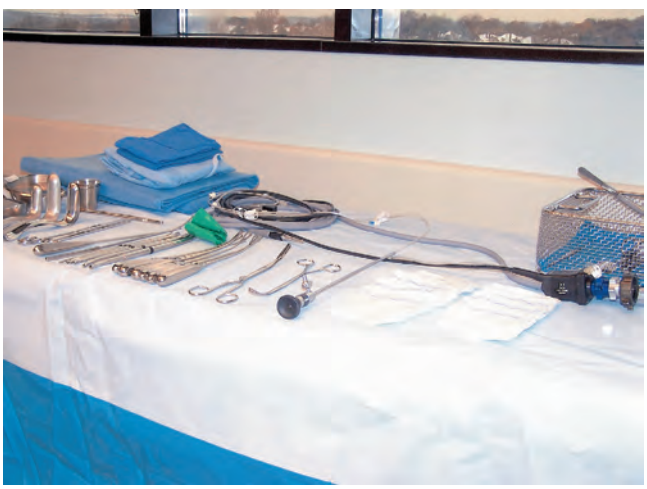


FIGURE 28.12 Hysteroscopy equipment. The back table contains a full hysteroscopic setup including retractors, dilators, tenacula, curettes, ovum forceps, diagnostic sheath, telescope, television camera, and light cable. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. Philadelphia: Lippincott Williams & Wilkins; 2007.)

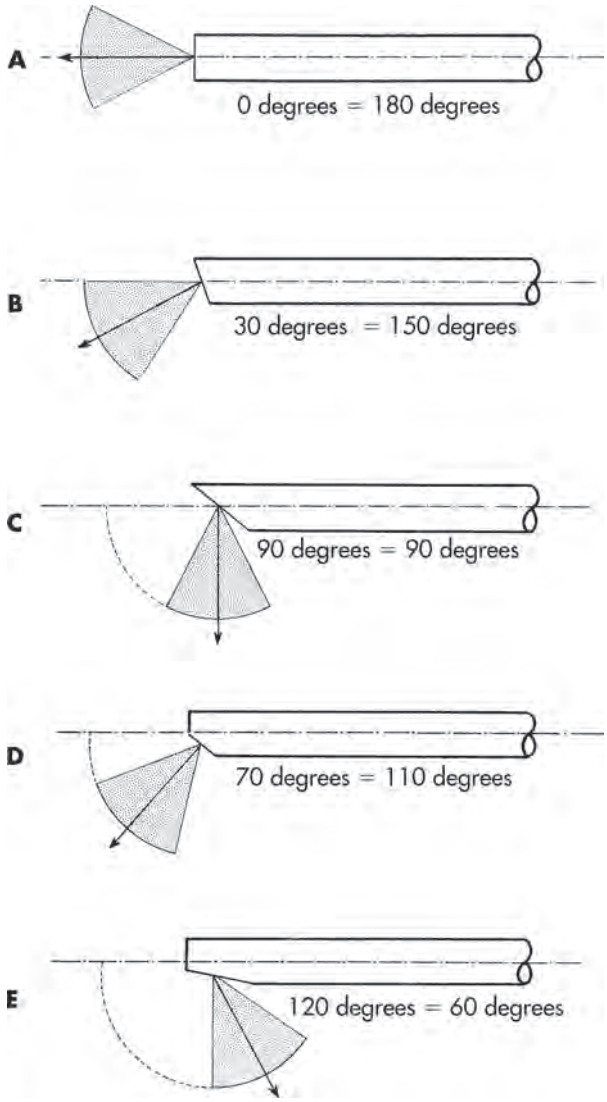


FIGURE 28.13 Hysteroscopes angles. Directions of view and angular notations of different endoscopes. Shaded areas show visual field. Direct or straight view **(A)**, fore-oblique view **(B)**, right angle view **(C)**, lateral view **(D)**, and retrospective view **(E)**. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. Philadelphia: Lippincott Williams & Wilkins; 2007.)

    - Rigid
      - 3 to 4 mm outer diameter
      - Inflow
- Sheath
  - 5 to 6 mm outer diameter
  - Continuous flow
  - Inflow and outflow port
  - Operative channel 3 fr, 5 fr
- Semirigid instruments
  - Scissors
  - Alligator forceps
  - Biopsy forceps
  - Tenaculum
- Light source from 100 to 300 watts
- Camera figure 2 camera, tower monitor (Fig. 28.14)
- Monitor

FIGURE 28.14 This endoscopic cart contains a light source, photographic equipment, and video monitor. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

- Distension media
  - Normal saline (most used nowadays)[62]
  - CO_2 (used sometimes for diagnostic hysteroscopy)
- Low–flow hysteroinsufflator
- Sterile gloves, cotton swabs, chlorhexidine gluconate or Betadine
- Instruments for anesthesia (paracervical block) operator preference

Procedure

Special Considerations

Patient selection is one of the most important requisites to have a successful procedure. Patients fear pain, discomfort, and an adverse diagnosis when an office hysteroscopy is scheduled.[61,66] A comprehensive written informed consent should be obtained in advance, and all questions answered and handouts given to patients. All patients need a documented last menstrual period and a negative pregnancy test. The perfect timing to do a hysteroscopy is during the proliferative phase of the menstrual cycle (first week after menses).[58,63,64]

There are multiple regimens to use for pain and discomfort management. In general, an NSAID (e.g., ibuprofen 800 mg orally, ketorolac 60 mg intramuscularly) and an anxiolytic if needed (e.g., diazepam 10 mg orally) are administered 30 to 60 minutes before the procedure.[66] Pain is associated with speculum insertion, tenaculum placement, paracervical block, and cervical dilation, all of which can be obviated if vaginoscopy (no touch approach) is used[58,63,64] (Fig. 28.15).

If cervical stenosis is suspected (postmenopausal, nulliparous women, after LEEP or cervical cone biopsy), the use of misoprostol 200 to 400 mcg is recommended 8 to 12 hours before the procedure. Misoprostol is a prostaglandin E1 that softens the cervix and facilitates the introduction of the hysteroscope.

Procedure in Detail[58] (Fig. 28.16)

1. Make sure all the equipment is properly working and attached.
2. Place the patient in the dorsal lithotomy position.
3. Perform a speculum and bimanual exam. If there is cervical discharge or the bimanual exam is painful, reschedule patient.
4. Clean the vagina and the cervix with chlorhexidine gluconate or Betadine.
5. Depending on physician preference, proceed with a vaginoscopy (no touch approach) or place a speculum to visualize the cervix.[63,64]
6. Using the continuous flow of distension medium (normal saline preferred) introduce the flexible or rigid hysteroscopy under direct visualization.
7. Identified both tubal ostia and make a conscious survey of the uterine cavity and cervical canal.

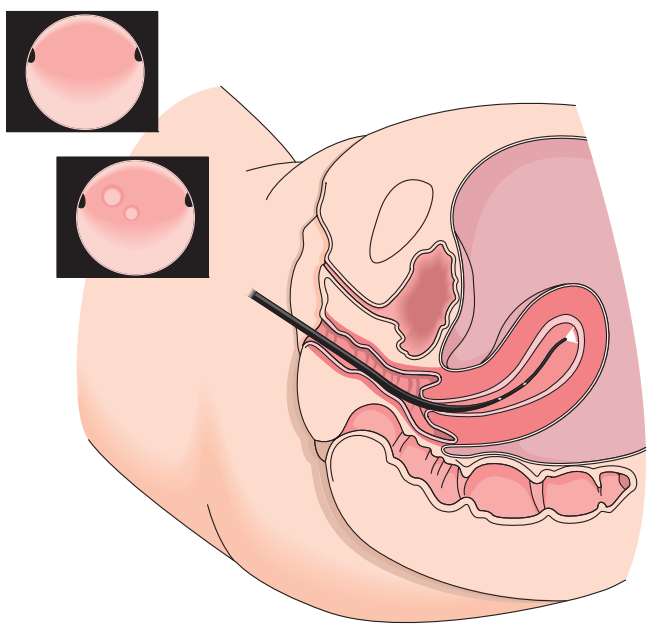


FIGURE 28.15 Vaginoscopy approach. (Courtesy of LifeART image copyright © 2014. Lippincott Williams & Wilkins. All rights reserved.)

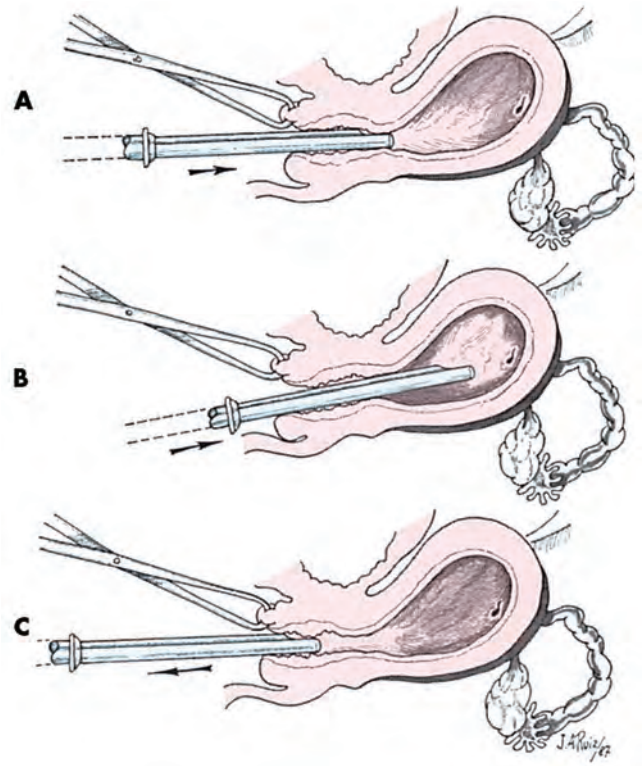


FIGURE 28.16 **A:** The endoscope is introduced at the level of the internal cervical os. **B:** The hysteroscope is advanced under direct vision to complete the examination. **C:** The endocervical canal is examined during withdrawal of the endoscope. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. Philadelphia: Lippincott Williams & Wilkins; 2007.)

8. Monitor fluid outflow to assure there is no more than 2500 mL of volume deficit when normal saline is used. Large volume deficit is very rare in diagnostic hysteroscopy.
9. Remove instruments and let the patient rest for several minutes.
10. Document procedure including indications, findings, size of hysteroscope used, distension media used, volume deficit if saline was used, duration of the procedure, patient tolerance, complications, specimen if biopsies were taken, and finally plan of care with follow-up.

Aftercare

If the patient did not receive sedation, anxiolytics, or narcotics, she is allowed to drive home or return to work immediately after the procedure. Patients may experience mild vaginal discharge and need to abstain from sex until the discharge resolves. The patient must be advised to call if bleeding/discharge persists or fever and pelvic pain develops.

Complications

- Cervical lacerations which increase bleeding and poor visualization in the uterine cavity.
- Creation of a false uterine passage with risk of bladder, vascular, or bowel injury.
- Uterine perforation. As soon a perforation is identified, the diagnostic portion of the hysteroscopy must be completed. Simple fundal perforations with minimal or not bleeding can be managed conservatively, but anterior, posterior, or lateral perforations require further investigation with laparoscopy or laparotomy, and cystoscopy if the perforation was anterior.
- Distension media complications in the office setting are very rare. Complications have been described with operative hysteroscopy and long surgical times of 60 to 90 minutes. In general, office diagnostic hysteroscopy is quick.[65]

HYSTEROSCOPIC TUBAL STERILIZATION

Tubal occlusion with Essure microinsert device is U.S. Food and Drug Administration (FDA) approved since 2002 after multiple clinical trials.[67] It is 99.74% effective (5 years) and consists of a 4-cm stainless steel inner coil and nickel titanium with polyethylene terephthalate outer implant placed in the proximal portion of the fallopian tube by hysteroscopy.[67,68] The tubal occlusion occurs by tissue ingrowth through the insert creating a natural barrier.[68] This procedure is commonly done in the office and is well tolerated by patients after a paracervical block.[63] Advantages and disadvantages are listed as follows.[67,69]

Advantages

- No incision
- Performed in an office setting
- Minimal to no anesthetic requirements
- Less postoperative pain
- Can be performed in women with extensive pelvic adhesions
- Can be performed in women with comorbidities

Disadvantages

- Need for contraception for 3 months after procedure until tubal occlusion is documented[70]
- Expense of device and imaging study to confirm tubal occlusion
- Higher risk of unilateral tubal occlusion
- Electrical conductivity of microinsert
- Special training and certification thru the Essure manufacturer

Indications

Permanent sterilization.

Contraindications

- Pregnancy
- Desire for future pregnancy

- History of previous tubal surgery including tubal ligation
- History of hydrosalpinx
- Severe intrauterine adhesions that prevents access to the tubal ostia
- Active or recent pelvic inflammatory disease
- Interval of less than 6 weeks following delivery, miscarriage, or pregnancy termination

Equipment

- Essure device—two individually wrapped devices (more should be available in case a device is damaged or does not deploy properly) (Fig. 28.17A)
- Hysteroscope—30-degree lens, fluid inflow, outflow, and instrument channel sheath
- Hysteroscopic grasper
- Normal saline (1000 mL bag prewarmed to 37°C) × 3
- Open-side speculum
- Tenaculum
- Camera, light source, and monitor

Preprocedure Preparation

- Two or more weeks prior to procedure: prescribe a progestin-containing contraceptive; depot medroxyprogesterone (Depo-Provera) is the preferred method because it will provide contraception for 3 months after the procedure when the HSG will confirm tubal occlusion.[71]
- Scheduling—early proliferative phase (improved visualization and decreased risk of luteal phase pregnancy)[71]
- Pregnancy test preprocedure
- NSAIDs preprocedure
- Do not sound
- Hydrodilate cervix
- Open-side speculum, remove after introducing scope if vaginoscopy is not performed
- Do not open Essure package until both ostia are visualized.
- It is recommended to have a backup Essure kit.

Procedure[67,69] (Fig. 28.17B,C)

- Confirm informed consent with patient.
- Medications at least 30 minutes before procedure: NSAID ketorolac 30 mg intramuscularly or ibuprofen 800 mg orally; Valium 10 mg orally if needed.
- Check equipment.
- Position and prepare patient for hysteroscopy.
- Perform hysteroscopy and visualize both tubal ostia, maintaining uterine distention.
- Placement and deployment:
  - Place the light post in the direction of the tubal ostia, insert and deploy the device.
  - Count and record the number of expanded coils extruding from the tubal ostia.
- Schedule low-flow HSG at 12 weeks after procedure.

Aftercare Recommendations

- Patients must be advised to call if experiencing fever, excessive vaginal bleeding, or severe or persistent pain.
- Patients may resume daily activities 1 day after procedure.
- Recommend the use of contraception for 12 weeks after procedure or until documented tubal occlusion by HSG.

Complications[67,69,72]

- Tubal or uterine perforation 1 to 3%
- Device expulsion less than 1%
- Incorrect placement diagnosed by HSG
- Contraceptive failure less than 1% at 5 years
- Fluid overload when fluid deficit is greater than 2500 mL normal saline
- Vasovagal reaction

Hysteroscopic tubal occlusion with Essure is well accepted by patients with more than 80% satisfaction, and most physicians feel comfortable performing the procedure after certification and five to six procedures done. Patient adherence to the recommended HSG at 12 weeks after the procedure to document placement ranges between 12 and 86%, making this issue a challenge for the provider. Some out of label uses of the Essure include tubal occlusion before IVF and management of bilateral hydrosalpinx.[73,74] Some have suggested the use of ultrasound to document correct placement of the device, instead of HSG.[75] Outside of United States, endometrial ablation is used simultaneously with Essure placement,[76] but in the United States, performing both procedures at the same time is not approved because endometrial ablation produces uterine synechiae, making HSG very difficult to interpret.[70]

If endometrial ablation is desired to control abnormal bleeding, the procedure should be done after there is a documented tubal occlusion.[70] Global endometrial ablation devices used after Essure are Thermachoice, NovaSure, and Hydro ThermAblator (HTA).[77]

After Essure placement, when electrosurgery needs to be used for hysterectomy or any other procedure, the provider must carefully avoid any tissue proximal to the cornua and proximal fallopian tubes.

GLOBAL ENDOMETRIAL ABLATION

Global endometrial ablation, also called second generation endometrial ablation, is a relative new technology to treat idiopathic heavy menstrual bleeding or dysfunctional uterine bleeding after medical management fails.[78] The idea is to destroy the endometrium and prevent or reduce menstrual bleeding.[79] Since its introduction in 1997, the FDA has approved five devices. In this segment, we will review those most commonly used in the office setting. Therma-Choice (thermal balloon

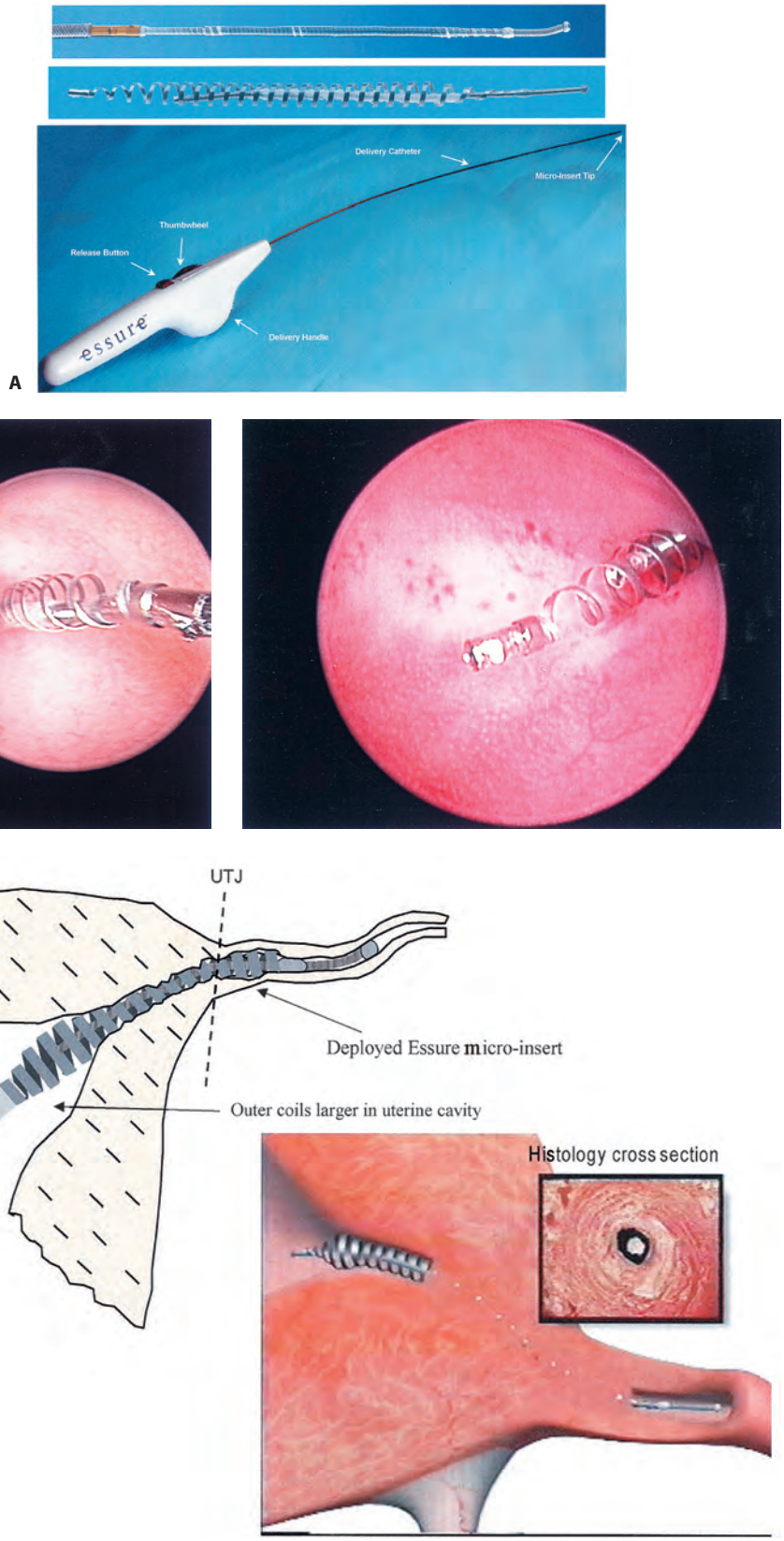


FIGURE 28.17 **A:** Unexpanded Essure microinsert (*top*), expanded microinsert (*below*), and deploying catheter with deliver handle (*bottom*). **B:** Essure microinsert's proximal tail in uterine cavity following hysteroscopic deployment. **C:** Diagrammatic representation of deployed microinsert and resultant tissue fibrosis 3 months after deployment. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. Philadelphia: Lippincott Williams & Wilkins; 2007.)

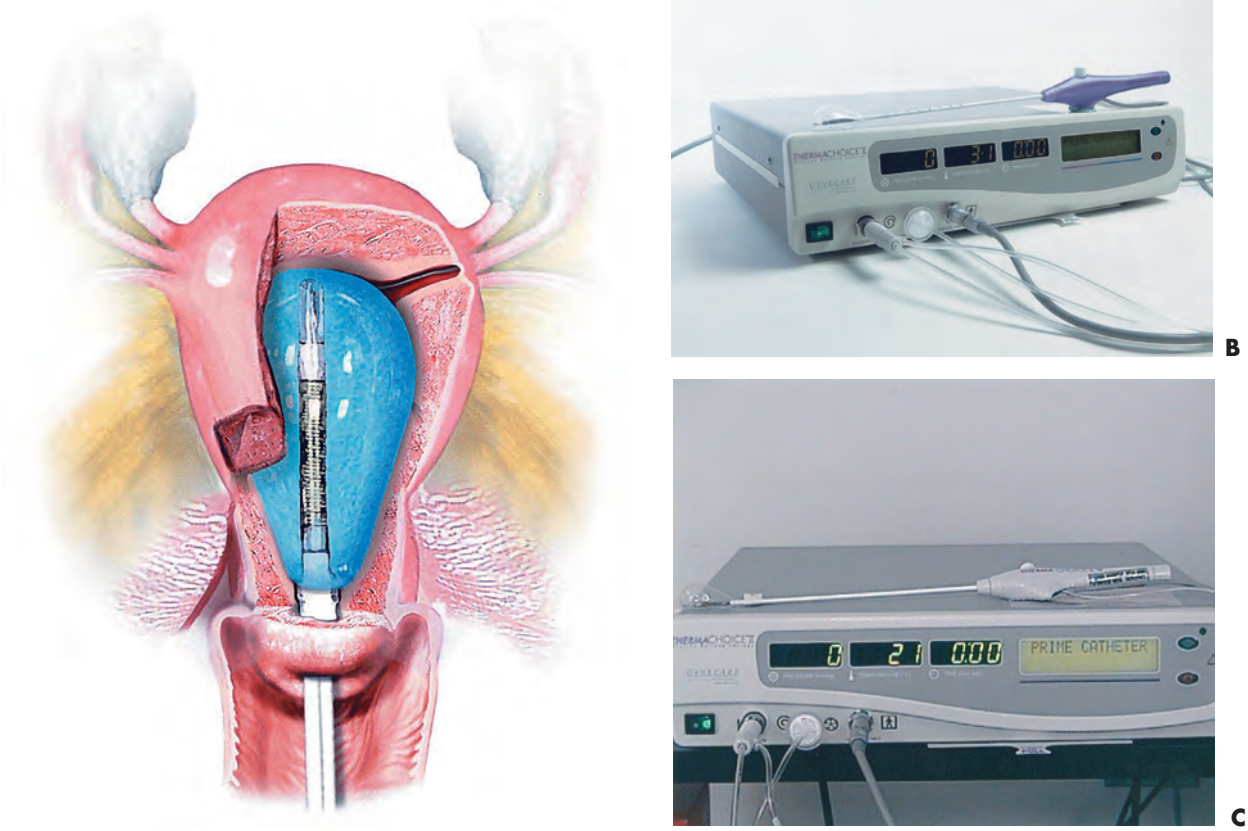


FIGURE 28.18 This cutaway illustration of the uterus shows a fully inflated balloon in place. **A:** The in situ heating coil is shown together with thermistors and pressure transducers. **B:** The Gynecare ThermaChoice II intrauterine balloon is shown here with its control unit. **C:** Magnified view of control unit panel of the control unit. Pressure is read out on the left, temperature within the uterine cavity is indicated in the center, and elapsed time on the far right panel. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

ablation) uses a heated fluid-filled intrauterine balloon (Figs. 28.18 and 28.19), Her Option Cryoablator (cryoablation) uses cryotherapy (Figs. 28.20 and 28.21), HTA (hydrothermal endometrial ablation) uses circulating heated normal saline (Fig. 28.22), and NovaSure (radiofrequency endometrial ablation) uses radiofrequency electrosurgical energy[78,79] (Fig. 28.23).

Office-based global endometrial ablation is safe, effective, fast, relatively painless, and easy to perform. It is cost-effective for the physician, patient, and payer. The majority of women undergoing office global endometrial ablation finds the procedure acceptable and would recommend the intervention to a friend with a similar problem. Discomfort during the procedure remains the main obstacle to more widespread implementation.[80]

Indications[81]

- Abnormal uterine bleeding due to benign disease.
- Nonpregnant and no plans for future childbearing. If patient is not sterilized, consider permanent sterilization before doing a global endometrial ablation.
- A desire to retain their uterus.
- No locally active infection.

FIGURE 28.19 **A:** The ThermaChoice cannula and inflated balloon are shown here. **B:** A magnified view of the inflated balloon and internal heating coil. The fluid is heated in situ within the distended balloon. The temperature is continuously monitored via the control unit. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

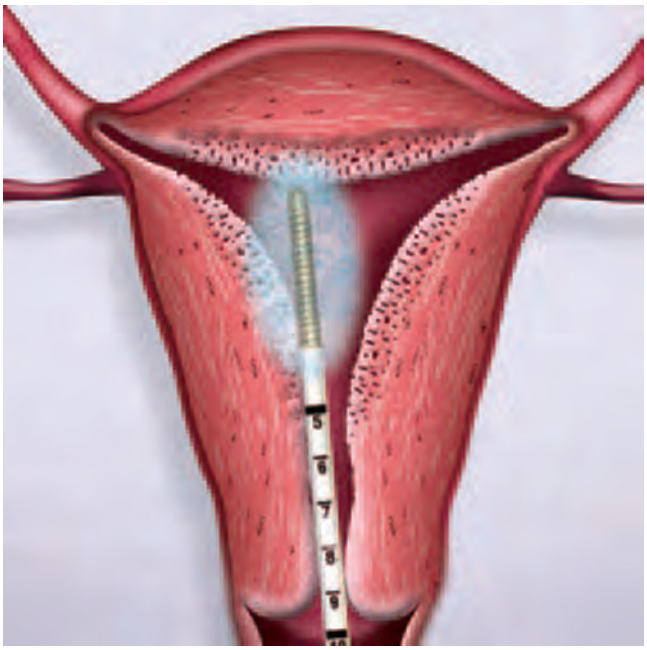


FIGURE 28.20 Cryoablation. Copyright © 2010 CooperSurgical, Inc.

Contraindications[78,81]

- Desire for future fertility
- Premalignant changes in the uterus or cervix
- IUD in place
- Congenital uterine abnormalities
- Active pelvic inflammatory disease or herpes
- Expectation or demand of amenorrhea
- Anatomic weakness of the uterus (prior classical C-section or transmural myomectomy)
- Postmenopausal bleeding
- Submucosal fibroids, polyps, or intramural fibroids greater than 4 cm
- Uterus greater than 10 cm if greater ablation will be done out label

Equipment[81]

The only devices that need special equipment are the HTA that requires a hysteroscopy in order to do the procedure and Her Option Cryoablation that requires ultrasound guidance.[82] It is recommended to have at least a saline infusion sonohystogram, a normal Pap smear, and a benign endometrial biopsy before any endometrial ablation. Some authors advocate for the use of diagnostic hysteroscopy before the procedure.[60]

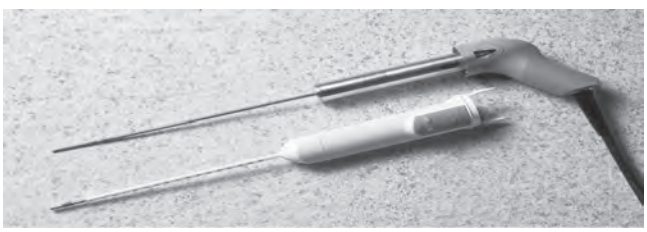


FIGURE 28.21 Equipment. Copyright © 2010 CooperSurgical, Inc.

Preprocedure Considerations

It is very important to set up expectations with the patient before the global endometrial ablation procedure. If relief of symptoms is the goal instead of amenorrhea, the majority of patients will be very pleased with the results. The patient needs to understand that she will feel some cramping and even pain during the procedure. Informed consent must be obtained before the procedure. The methods and outcomes must be reviewed with the patient the day of the procedure. Patients should expect to leave the office in 3 hours and have a driver (or someone to pick her up) after the procedure. Schedule the procedure in the early proliferative endometrial phase.

Procedure

- Give NSAIDs at least 12 hours before the procedure (Ibuprofen 800 mg).
- Thirty minutes before procedure, give patient antiemetic Phenergan 25 mg IM, acetaminophen/hydrocodone 500/7.5 mg PO, diazepam 10 mg PO, Toradol 60 mg IM.
- Perform speculum and bimanual exam.
- Perform a paracervical block. Deep nerve block with this procedure is essential.
- Perform a hysteroscopy exam and sound the uterus.
- Use the global endometrial ablation device of your choice: Therma-Choice, Hydro ThermAblator, or NovaSure. Use of all the devices requires training by the manufacturer, but in general, they are very user friendly.[82]
- Her Option uses a cryoprobe that causes endometrial cell death through freezing and is used under ultrasound guidance.
- All the procedures last between 90 seconds and 10 minutes.

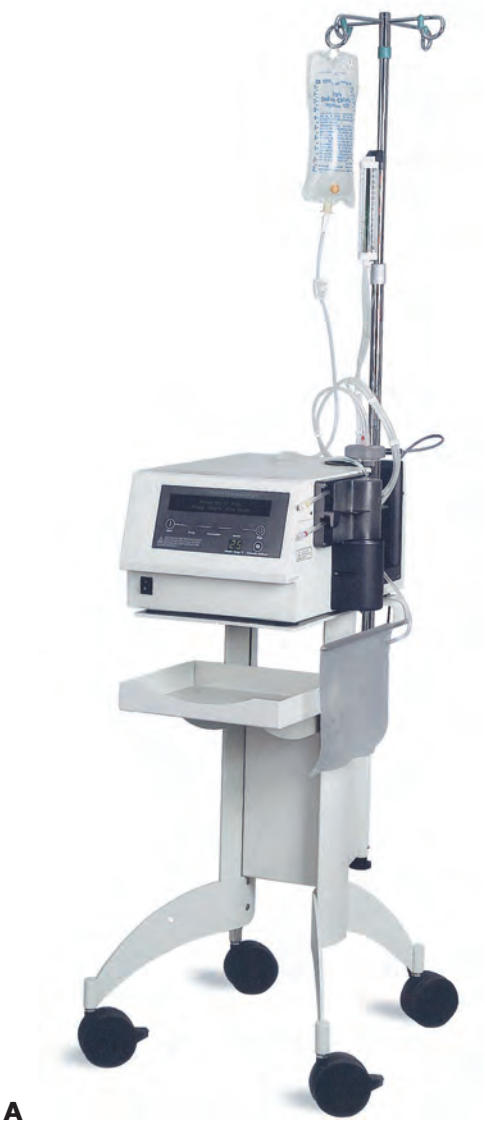
After Procedure Instructions

Medications

- Take Motrin 200 mg four tablets every 8 hours for 24 hours, then as needed for pain.
- Take Vicodin 5/500 mg one tablet every 6 hours for 24 hours, then as needed for pain.
- Take Phenergan 25 mg suppository for nausea.

Recommendations

- Discomfort is usually most significant 2 to 6 hours after ablation. A heating pad to the abdomen can provide additional relief. Patient needs to notify provider



A

B

C

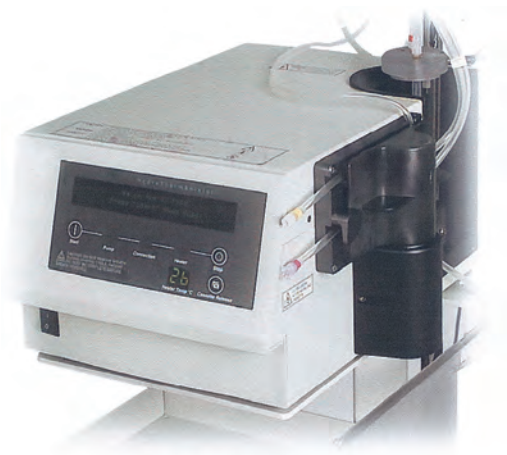


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FIGURE 28.22 **A:** The Hydro ThermAblator (HTA) control unit with reservoir bag of normal saline flowing into the heating unit. **B:** Magnified view of the outside-the-uterus heating unit. **C:** The hysteroscope and sheath that deliver the hot saline into the uterus under direct vision. **D:** The control unit measures intrauterine fluid, pressure, and temperature. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

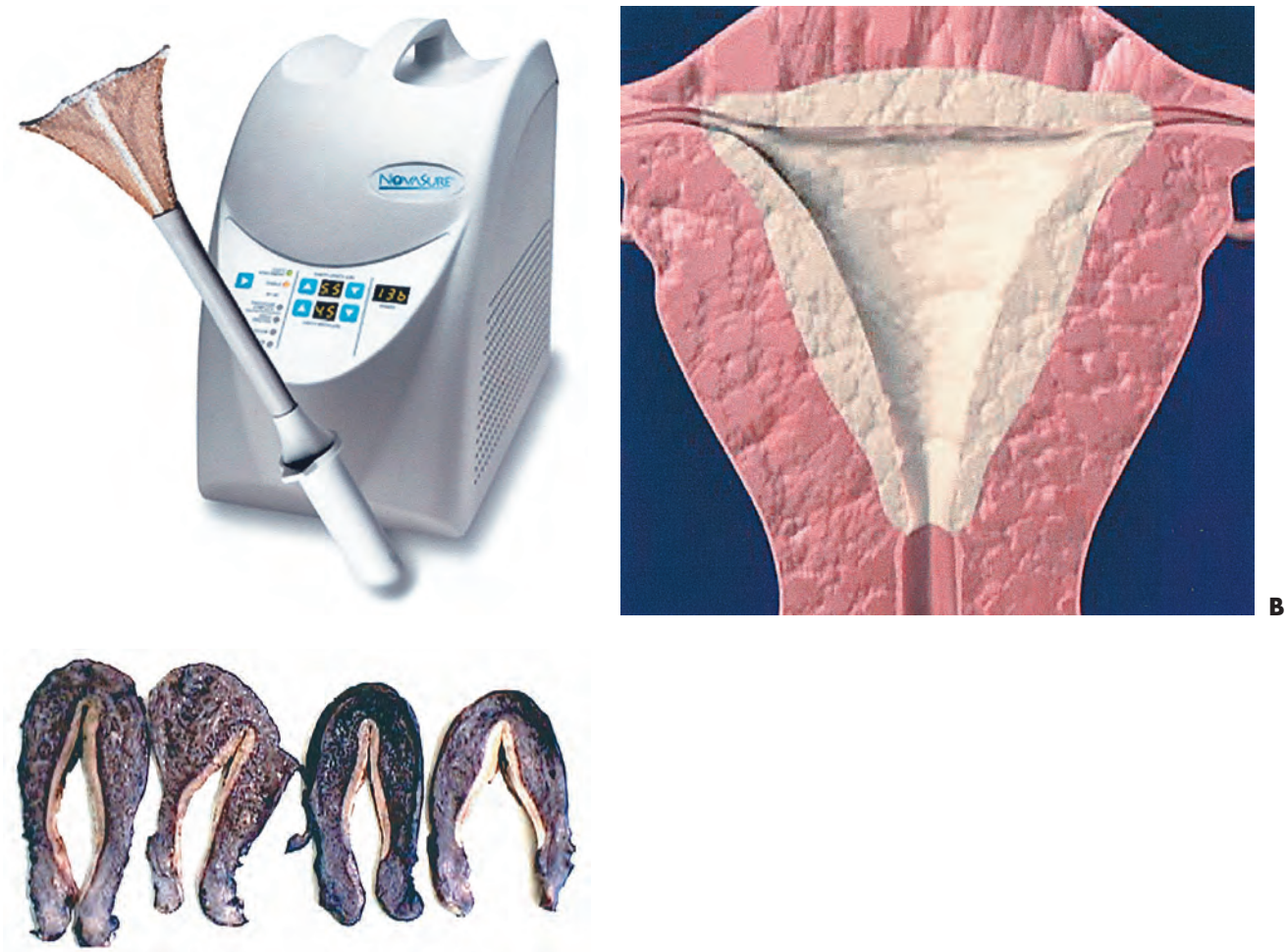

FIGURE 28.23 **A:** NovaSure device and bipolar generator unit. The intrauterine bag is porous mesh-like and sucks the wall to the bag. **B:** Model showing the well-defined schema of thermal coagulation. **C:** Actual whole uterine section showing the yellow thermal necrosis pattern. (From Baggish MS, Valle RF, Guedj H. *Hysteroscopy: Visual Perspectives of Uterine Anatomy, Physiology and Pathology.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2007.)

of severe pain that is not well controlled by pain medications.

- Fever may be a sign of infection. Patient should take her temperature two to three times daily for the first 3 days. If temperature is 100.6°F or more during the first 3 days after procedure, they must call the provider.
- Nausea may occur for the first 4 to 6 hours following the procedure. It usually can be controlled with Phenergan suppositories (one suppository every 4 to 6 hours).
- Vaginal discharge following this procedure can be variable. Anything from a watery discharge with occasional blood staining, passage of clumps of gray tissue, to menstrual-like bleeding for up to 4 weeks is normal. Patients may also have a minimal discharge. Tampons must not be used for the first week following thermal ablation. No intercourse for at least a week after, or until the discharge decreases, whichever happens first.
- Work may be resumed 2 days after procedure.

Complications[82,83]

- Intrauterine scarring with cervical stenosis
- Pain-related obstructed menses (hematometra, postablation tubal sterilization syndrome)
- Uterine perforation
- Pregnancy after endometrial ablation
- Failure to control menses (repeat ablation, hysterectomy)
- Risk from pre-existing conditions (endometrial neoplasia)
- Infection
- Equipment failure

Outcome of Second-Generation Endometrial Ablation at 24 Months[84]

- Patient satisfaction 90%
- Additional surgery within 2 years 8.5%
- Nausea and vomiting 15%
- Hemorrhage 2%

- Hematometra 1.4%
- Endometritis 1.8%
- Myometritis 0.4%
- Pelvic inflammatory disease 1.1%
- Fever 1.0%
- Cervical laceration 1.0%
- Perforation 0.7%
- Hydrosalpinx 0.4%
- Amenorrhea 38%

Efficacy[81,85]

- Wait 8 to 12 weeks to evaluate results.
- Hysterectomy rates range from 9 to 24% 3 to 5 years after the procedure.
- Endometrial re-ablation ranges from 5 to 20% 3 to 5 years after the procedure (global ablation should never be performed again).
- Her Option and NovaSure have documented success rates of 90% after 3 years.
- Thermachoice has 80% documented reduction in irregular bleeding in 5 years.

It is important to remember that second-generation global endometrial ablation is not a sterilization procedure, and patients will need contraception if permanent sterilization was not performed before the procedure.[82,86] Further work is required to improve the patient experience, identify women likely to tolerate the procedure well, and most importantly, minimize pain while maintaining a simple, safe, and convenient approach suitable for the office setting.

Office procedures in gynecology is a growing part of gynecologic practices, more and more procedures will move from the operating room to the office and it is in the best interest of practitioners to be in the vanguard of this trend.

CLINICAL NOTES

- It is preferable to have a special room for office-based procedures and identified staff dedicated to the offered procedures.
- The practitioner needs to ensure the creation of protocols, checklists, and policies within the practice that will assure the success of more invasive and technological difficult procedures.
- There are different levels of anesthesia (pain control): Level 1 is local anesthesia with minimal or no preoperative oral anxiolytic medication, level 2 is moderate sedation, and level 3 is deep sedation or general anesthesia. Most office procedures are done using level 1 anesthesia.
- Innervation of the uterus and cervix arise from the S2–S4 roots and nerves travel to the uterus in the lower portion of the broad ligament to the paracervical ganglion, which is the target for paracervical block anesthesia.
- The technique of paracervical block itself is not standardized but beneficial techniques include use of carbonated lidocaine, deep injection to 3 cm, a four-site injection, slow injection (over 60 seconds), and waiting 3 to 5 minutes before the schedule procedure.
- Local anesthetic toxicity and intravascular injection may occur with paracervical block and can produce a vasovagal reaction, convulsions, cardiac arrhythmias, and respiratory arrest. A metallic taste in the mouth may be an early warning sign of systemic toxicity.
- Permanent resolution of a Bartholin cyst usually occurs following an I&D with Word catheter placement and marsupialization. If an abscess or signs of significant cellulitis are present, a broad-spectrum antibiotic should be used after the procedure.
- General contraindications to IUD placement are pregnancy, uterine abnormalities causing distortion of the endometrial cavity, acute cervicitis or pelvic inflammatory disease, postpartum endometritis or infected abortion in the past 3 months, abnormal uterine bleeding of unknown etiology, women with multiple sexual partners, and a history of a prior ectopic pregnancy.
- Patient should be examined 1 month after placement of an IUD to confirm appropriate placement by visualizing the strings.
- The major risk of infection with IUD use is at the time of insertion and does not increase with long-term use.
- Early location of the pregnancy is important in women with a known IUD in situ to rule out an ectopic pregnancy.
- After an endometrial biopsy, allow the patient to remain supine on the examining table for a couple of minutes after the procedure to avoid any vasovagal reaction.
- If delayed post-LEEP bleeding that is heavy and not related to menses is encountered, the patient will need to be evaluated. Use of Monsel solution, silver nitrate, electrocautery, or packing usually provides adequate hemostasis.
- A brown discharge can be expected for at least 2 weeks after an LEEP.
- The perfect timing to do a hysteroscopy is during the proliferative phase of the menstrual cycle (first week after menses).

(continues)

- Hysteroscopic tubal occlusion with Essure is well accepted by patients with more than 80% satisfaction, and most physicians feel comfortable performing the procedure after certification and five to six procedures done.
- Patient adherence to the recommended HSG at 12 weeks after hysteroscopic tubal occlusion to document placement ranges between 12 and 86%.
- It is very important to set up postprocedural expectations with the patient before a global endometrial ablation procedure. If relief of symptoms is the goal instead of amenorrhea, the majority of patients will be very pleased with the results.
- Global endometrial ablation is not a sterilization procedure, and patients will need contraception if permanent sterilization was not performed before the procedure.

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SECTION V

Office Management Issues

CHAPTER 29

Patient Safety in Ambulatory Gynecology

Tejal Gandhi and Roxane Gardner

Much energy has been directed toward improving patient safety in acute care settings since the year 2000 when the Institute of Medicine (IOM) published their landmark report on medical error *To Err Is Human*, declaring their support for a comprehensive approach to improving patient safety.[1] During that same year, leaders of the American College of Obstetricians and Gynecologists (the College) formed a subcommittee on patient safety to affirm their professional organization's commitment to such endeavors. Since 2004, national attention has turned toward improving patient safety in the office and outpatient surgery settings.[2,3] The College's Committee on Patient Safety and Quality Improvement redoubled its efforts in 2008 to make patient safety in the office setting a priority.[4] Patient safety should be incorporated into every aspect of office-based care.[5] This chapter provides an overview of medical errors and adverse events in office gynecology, explores factors that contribute to their occurrence, and addresses efforts aimed at preventing their occurrence or mitigating their effects. Specific clinical approaches toward improving quality and safety of outpatient procedural care are also addressed.

GENERAL CHARACTERISTICS AND TRENDS IN OFFICE-BASED PRACTICE

Major shifts toward providing more health care services in the office and outpatient surgery centers are driving efforts to ensure safe patient care is delivered in such settings. The National Center for Health Statistics estimated that 1.1 billion patient care visits were made to physicians in the office, hospital emergency rooms, and outpatient departments during 2006.[6] About 80% of these office visits were distributed among primary care physicians (46.8%), medical specialists (17.7%), and surgical specialists (15.8%). About 18% of all visits involved routine checkups and prenatal exams. At least one medication was prescribed or continued in 7 of 10 office visits, with analgesics being the most common of the therapeutic categories. Of the estimated 902 million visits made to office-based physicians during 2006, about half were with primary care providers, a category that includes obstetrician-gynecologists.[7] However, obstetrician-gynecologists comprised about 8% of all office-based physicians. Notable trends identified during the 2005 to 2006 survey of office-based physician practices included the following:

- A shift toward multispecialty group practice
- Greater use of midlevel providers
- Physicians working fewer hours
- An increase in the number of female physicians from 19.4% in 2001 to 2002 to 24.1% in 2005 to 2006[8]

Multispecialty group practices averaged more physicians than solo or single-specialty practices; used more midlevel providers; and provided onsite laboratory testing, imaging studies, and therapeutic services more frequently.

Similar changes were identified in the practice profile of obstetrician-gynecologists. Findings from the most recently published report from the College in 2003 identified a statistically significant increase in the mean age and experience of physicians, a dramatic increase in the proportion of women physician, and a striking shift away from solo practice.[9] More recent findings from

the 2008 unpublished report reveal these trends have continued.[10] The practice of obstetrics and gynecology has long been primary care–oriented and will become increasingly focused on managing health care needs of an older population as the average lifespan increases and our baby-boom population ages.[11-13]

Office Practice–Related Issues and Demands Contributing to Patient Harm

Current trends in the growth of office-based practice, a broader scope of services provided in such settings, and the demands inherent to clinical practice can affect the safety and quality of patient care. Research aimed at identifying and characterizing human- and system-based factors that affect patient safety in office practice has begun to emerge.[14-16] Veltman[17] recently reviewed practice-related issues and demands that contribute to harm in obstetrics. These findings, with some modification, are applicable to office practice in obstetrics and gynecology (Tables 29.1 and 29.2).

Whether occurring in isolation or in some combination, these issues and demands serve to make clinical office practice vulnerable to error. Physicians often feel pressured to be in more than one place at the same time by seeing patients in the office, in the hospital, and in the outpatient surgery centers. Economic pressures driving physicians to see more patients in a shorter amount of time can lead to off-site monitoring of high-risk clinical situations or performing procedures in the office when patients are more appropriate for hospital-based inpatient or outpatient procedures. Fortunately, most patients are healthy. However, the demographic shift toward an aging population means more patients with a greater likelihood of having comorbidities and chronic illness such as diabetes, hypertension, asthma, or obesity will be presenting for care. Acute deterioration in a patient's clinical condition during a routine office visit or an office-based surgical procedure will consume that physician's time and attention while managing the situation, potentially interfering with clinical care provided to other scheduled patients. Managing unexpected situations like these or dealing with other work-related interruptions or personal matters will complicate the normal flow of daily office care and may adversely affect patient safety.[18]

Protocols guiding handoffs, sign-outs, test result follow-up and referrals, consultations, or patient transfers may be inadequate or nonexistent in the office setting, thus increasing vulnerability to medical error.[17,19,20] Poor teamwork and office hierarchies can further undermine defenses to error.[21] Additional human factors related to postcall fatigue, the status of one's own personal health or other personal circumstances can affect concentration and potentially impair the clinician's cognitive decision making or technical skills.[22,23] Moreover, being overly confident about managing a specific clinical situation or patient-related circumstance or making exceptions or yielding to demands made by patients may facilitate error and patient harm.[17,24]

TABLE 29.1 Practice-Related Issues Contributing to Patient Harm

Issue	Example
Regional variation in office-based office and surgical practice	Deficient or inadequate guidelines, policies, or procedures Lack of adherence to guidelines, policies, or procedures
Uncertainty in clinical care	Presentation Diagnosis Risk assessment Management Response to treatment
Resource limitations	Staff Space Equipment Time
Wishful thinking	"Fallacy of the low-risk patient"—continuing to perceive and manage a patient as low risk when their clinical circumstances have become high risk

Modified from Veltman L. Getting to Havarti: moving toward patient safety in obstetrics. *Obstet Gynecol.* 2007;110(5):1146–1150.

TABLE 29.2 Inherent Demands Weakening Defenses to Error

Inherent Demands of Clinical Practice

- Presence demanded in more than one place at the same time
- High clinical volume, largely normal patients
- Increasing growth in population of elderly patients with comorbidities
- Off-site monitoring of high-risk clinical situations
- Poor sign-out
- Inadequate protocols for referrals, consultations, or patient transfers
- Impaired vigilance-distractions, fatigue, etc.
- Hierarchical operations, poor teamwork
- Yielding to patient pressures regarding clinical practice
- Overconfidence (hubris)

Modified from Veltman L. Getting to Havarti: moving toward patient safety in obstetrics. *Obstet Gynecol.* 2007;110(5):1146–1150.

Liability in Office-Based Practice

Malpractice data is the tip of the iceberg when looking at where medical errors occur. However, analysis of these cases sheds light on breakdowns in the processes that contribute to patient harm and reveal opportunities where improvements can be implemented. Allegations of missed or delayed diagnosis featured prominently in a review conducted during 2007 by the Controlled Risk Insurance Company/Risk Management Foundation (CRICO/RMF) of the Harvard Medical Institutions.[25] CRICO/RMF found that 623 office-based malpractice cases comprised 27% of total malpractice cases alleged across all medical and surgical specialties between 1997 and 2006. Missed or delayed diagnosis of a clinical condition was alleged in 324 (52%) of these office-based cases. Failure or delay in ordering

TABLE 29.3 Clinical Care Issues Identified in CRICO/RMF Office-Based Malpractice Cases

Clinical Care Issues in Office-Based Malpractice Cases
Poor clinical judgment
• Failure/delay in ordering a test
• Narrow diagnostic focus
• Failure to obtain consult/referral
• Failure to establish differential diagnosis
• Patient assessment—inadequate history/physical
• Poor selection/management of medication
• Failure to follow up on an abnormal finding
Poor clinical systems
• Patient follow-up
• Reporting findings
• Identifying provider coordinating care
Inadequate communication
• Patient information among providers
• Relaying information to patient
• Insufficient patient education about medications
• Inadequate documentation

CRICO/RMF, Controlled Risk Insurance Company/Risk Management Foundation.

a diagnostic laboratory test was alleged in 62% of all diagnostic error cases and 56% alleged poor follow-up of a plan and, if indicated, a referral. After diagnostic errors, 84 of 623 office practice cases (14%) involved medication errors; this was followed by 24 cases (4%) alleging mismanaged medical treatment, 24 cases (4%) alleging miscommunication, and 20 cases (3%) with surgery-related allegations. The major clinical conditions identified in CRICO/RMF's office-based cases were cancer, infection, myocardial infarction, benign tumor, or stroke. The predominant clinical care issues in these cases involved poor clinical judgment, poor clinical systems, inadequate communication, and poor documentation (Table 29.3).

Gandhi et al.[26] conducted an in-depth review of closed malpractice claims from four independent malpractice insurance companies in which missed or delayed diagnosis was alleged in the ambulatory setting. They found 181 of 307 (59%) cases involved diagnostic errors that harmed patients. Cancers, primarily breast and colorectal, were the leading clinical diagnoses in 106 of 181 (59%) cases. Failure to order appropriate tests, failure to create a proper follow-up plan, failure to obtain an adequate history or perform an adequate physical examination, and incorrect interpretation of diagnostic tests accounted for breakdowns seen in the process of care along the diagnostic pathway. They noted that the leading factors contributing to these errors were failures in judgment, inadequate vigilance or memory, knowledge deficits, poor handoffs, and patient-related factors such as noncompliance with follow-up plans. They found that 107 of 181 (59%) diagnostic error cases had three or more of these contributing factors. Although few cases could be linked to a single contributing factor or breakdown in the process of care, most diagnostic errors that harmed patients resulted from the alignment of multiple breakdowns that stemmed from the synergy of contributing factors. The authors concluded that being aware of the most common types of breakdowns and factors contributing to their occurrence could facilitate the design and prioritization of strategies to prevent diagnosis-related errors in ambulatory care settings.

Liability Identified in Gynecologic Office-Based Practice

CRICO/RMF recently conducted an analysis of all gynecology claims contained within their Comparative Benchmarking System (CBS) asserted between the years 2004 and 2008.[27] CBS is a repository of data from open and closed medical malpractice claims and suits reported by a subset of academic medical centers, community-based hospitals representing over 20 states, and leading commercial insurers and captives. A total of 472 gynecology cases were asserted during this 5-year period, with 241 inpatient cases, 197 outpatient cases, and 34 cases whose location of origin was unclear. Of the 197 outpatient cases, 88 cases (45%) involved office-related care and 81 cases (41%) involved ambulatory surgery-related care.

The majority of the office-based cases alleged errors in diagnosis, 61/88 (69%); this was followed by alleged errors in medical treatment (15%), obstetric care (3%), communication (2%), medication (2%), and surgical treatment (2%) (Table 29.4).

Risk management issues frequently seen in the diagnostic error-related cases involved the ordering of diagnostic or laboratory tests (52%), followed by issues related to history taking and physical examination (41%), and interpretation of tests (41%) (Table 29.5). Cancer was the dominant clinical condition in diagnostic error-related cases, including cancer of the breast, cervix, uterus, and ovary. Complications related to pregnancy such as ectopic pregnancy and missed abortions were seen but less frequently (Table 29.6).

TABLE 29.4 Major Allegations in Gynecologic Malpractice Claims Involving Office-Based Care

Major Allegations Involving Office-Based Care	# Cases (%)
Diagnosis-related	61 (69%)
Medical treatment	13 (15%)
OB-related treatment	3 (3%)
Communication	2 (2%)
Medication-related	2 (2%)
Surgical treatment	2 (2%)
Breach of confidence	1 (1%)
Hospital policy and procedure	1 (1%)
Provider behavior	1 (1%)
Pending classification	2 (2%)
Total	**88 (100%)**

From Comparative benchmarking system [database]. Cambridge, MA: CRICO/Risk Management Foundation of the Harvard Medical Institutions; 2010. Updated August 5, 2010.

TABLE 29.5 Risk Management Issues Identified in Gynecologic Malpractice Claims Involving Diagnostic Error-Related Cases

Risk Management Issues in the Diagnostic Process of Care	# Cases (%)
History/physical and evaluation of symptoms	25 (41%)
Order of diagnostic/lab tests	31 (52%)
Performance of tests	1 (2%)
Interpretation of tests	25 (41%)
Receipt/transmittal of test results	10 (16%)
Physician follow up with patient	16 (26%)
Referral management	9 (15%)
Patient compliance with follow-up plan	9 (15%)
Total	**61 (100%)**

From Comparative benchmarking system [database]. Cambridge, MA: CRICO/Risk Management Foundation of the Harvard Medical Institutions; 2010. Updated August 5, 2010.

The ambulatory surgery-based cases were most notable for allegations involving error in surgical treatment, whereas relatively few cases contained allegations of errors in medical treatment, diagnosis, and equipment (Table 29.7).

THE ROLE OF SAFETY CULTURE IN THE AMBULATORY SETTING

Creating a culture of safety is essential in the office setting regardless of specialty.[28,29] As stated by the IOM,[30]

TABLE 29.6 Final Clinical Diagnosis Identified in Gynecologic Malpractice Claims Involving Diagnostic Error-Related Cases

Final Clinical Diagnosis in Gynecologic Diagnostic Error Cases	
Cancer	48
Breast	19
Cervix	11
Uterus	9
Ovary	4
Other female genital organs	2
Liver and intrahepatic bile duct	1
Other organs of the gastrointestinal tract	2
Complications mainly related to pregnancy	4
Ectopic pregnancy	3
Missed abortion	1
Anxiety states	2
Unspecified neoplasms	2
Diseases of female genital organs/female infertility	2
Anemia	1
Secondary malignancies	2
Abortion-related disorders	2
Contraceptive-related issues	1
Total	**61**

From Comparative benchmarking system [database]. Cambridge, MA: CRICO/Risk Management Foundation of the Harvard Medical Institutions; 2010. Updated August 5, 2010.

TABLE 29.7 Major Allegations in Gynecologic Ambulatory Surgery-Based Care

Major Allegations Involving Ambulatory Surgery Care	# Cases (%)
Surgical treatment	65 (80%)
Medical treatment	8 (10%)
Diagnosis-related	3 (4%)
Equipment	2 (2%)
Hospital policy and procedure	1 (1%)
Communication	1 (1%)
Medication-related	1 (1%)
Total	**81 (100%)**

From Comparative benchmarking system [database]. Cambridge, MA: CRICO/Risk Management Foundation of the Harvard Medical Institutions; 2010. Updated August 5, 2010.

"All health care settings should establish comprehensive patient safety programs operated by trained staff within a culture of safety." The IOM[30] defines a safety culture as "an integrated pattern of individual and organizational behavior, based upon shared beliefs and values, that continuously seeks to minimize patient harm that may result from the process of care delivery." Safety culture is the constant commitment to safety as a top priority permeating the entire organization. A safety culture is one that

- Acknowledges the high-risk, error-prone nature of an organization's activities
- Provides a blame-free environment where individuals are able to report errors or close calls without punishment
- Recognizes that most errors are from good people working in bad systems ("not bad apples")
- Demonstrates organizational willingness to direct resources to address safety concerns. Elements of an ideal culture of patient safety are highlighted in Table 29.8.

The IOM acknowledged that the biggest challenge to moving toward safer care is changing our culture from blaming and shaming providers for their errors to a culture where errors are seen as opportunities to improve the system and prevent harm to patients.[31] Culture change cannot be mandated. It develops over time and requires persistence. Success is more likely when key individuals help design new approaches that solve

TABLE 29.8 Elements of an Ideal Culture of Patient Safety

1. Shared beliefs and values about the health care delivery system
2. Recruitment and training with patient safety in mind
3. Organizational commitment to detecting and analyzing patient injuries and near misses
4. Open communication regarding patient injury results
5. Establishment of a just culture: willingness to report near misses and adverse events without threat of retribution, balancing the need to learn from such events with the need to take disciplinary action

Adapted from Aspden P, Corrigan JM, Wolcott J, et al, eds. *Patient Safety: Achieving a New Standard for Care*. Washington, DC: National Academies Press; 2004.

TABLE 29.9 Patient Safety Essentials for an Office Practice

Essentials for an Office Practice	Strategies
Create a culture of safety	Leadership support Culture measurement
Create mechanisms to identify risk	Reporting systems, focus groups, ambulatory M&M or case review
Analyze near misses and adverse events from a systems perspective	Develop knowledge in human factors and systems Learn how to design and implement robust process improvements
Feedback to staff about improvements	Staff meetings, newsletters

M&M, morbidity and mortality.

real problems. As staff members realize that these new approaches yield positive results, then the values and new behaviors become "the way we do things around here." The College strongly advocates "integrating a patient safety culture into every standing committee, every agenda, and every educational opportunity provided to Fellows."[32] Several key steps to implementing patient safety culture and improvements in the ambulatory setting are described in Table 29.9.

Assessing Safety Culture

There are tools specifically designed to assess safety culture in the office setting, identifying how staff members perceive their environment and shedding light on specific areas in need of improvement. Results from periodic reassessment can provide insight about the impact of interventions aimed at improving safety culture. Safety culture assessments obtained at a variety of offices within a large group practice or health care system can be used to characterize and compare how patient safety is perceived at each of these locations. The Agency for Healthcare Research and Quality (AHRQ) sponsored the development of patient safety culture assessment tools for ambulatory outpatient medical offices as well as for nursing homes and hospitals.[33] The "Medical Office Survey on Patient Safety Culture" was developed in response to medical offices interested in having a survey that focuses on patient safety culture in their offices. This survey is designed specifically to assess safety culture and health care quality as perceived by office-based providers and staff who work in an office having at least three providers (physicians, physician assistants, nurse practitioners, and other medical providers) licensed to diagnose medical problems, treat patients, and prescribe medications. Survey administration in solo or two-provider office settings is not recommended because it would not be possible to maintain the confidential nature of individual responses. In small offices, rather than administering the survey, it can be used as a tool to initiate open dialog or discussion about patient safety and quality issues among providers and staff. This tool is readily available on the AHRQ website.[33]

The Role of Leadership in Promoting Patient Safety Culture in Office Practice

Leadership support is essential because leaders, whether in the office, the outpatient surgery facility, or the hospital, set the tone for acceptable behaviors and actions in the workplace.[34] Leadership needs to believe in a nonpunitive culture with a systems approach to error. Leadership should attend safety conferences or meet with staff regularly to discuss safety issues. Mechanisms need to be in place to report adverse events and near misses (such as reporting systems, focus groups, outpatient morbidity, and mortality conferences), and staff should feel secure in reporting and understand that errors are most commonly due to bad systems, not bad people. For reporting errors and near misses, staff should be rewarded, not reprimanded or punished. In addition, leadership needs to act on errors and make changes, so that staff perceives that the focus of reporting is on improvement and error reduction. Feedback should be given to staff so they understand exactly what improvements have been made to benefit patient safety.[35] Policies and processes need to be implemented to empower error reduction. Transparency to patients is also essential, including leadership supported disclosure of errors and adverse events to patients.[36,37] Finally, creating support systems for patients, families, and physicians who encounter errors is also important. All of these strategies require leadership commitment and will ultimately lead the office practice to a culture that will optimize patient safety.

A Systems Approach to Error

A key issue in creating a systems approach to error is efficiently translating data into action. Compiling errors is useful only if the results are to improve system safety. Office practices need to develop skills in analyzing events, understanding root causes, and designing and implementing system improvements. Ideally, multidisciplinary teams (nurses, pharmacists, and physicians) should analyze events to maximize the learning process. Health care has traditionally focused on individuals and individual performance. However, human factors experts note that it is more effective to change the system as a whole rather than focus on individual blame.[38] The objectives of systems designed for safety are to make it difficult for individuals to make errors and to catch errors that do occur in order to minimize their impact. The first step in systems analysis is to identify the systems failures that allowed the errors to occur. These failures need to be evaluated for factors that contributed to the error. These contributing factors have been well described in health care and include issues with teamwork, communication, staffing, work environment, and equipment.[39] When evaluating these factors, questions should be asked such as, "How commonly does this occur?" "What is the potential impact on safety?" and "What are feasible strategies for improvement?"

Classifying events by the type of error and the systems that contributed to the error can help guide subsequent projects. Once contributing factors have been identified, organizations and processes need to be evaluated for changes that can reduce the likelihood of these contributing factors occurring and leading to errors. Once improvement projects are identified, responsibility and accountability must be assigned to individuals empowered to create change. The only way to ensure that action will occur is if people feel responsible and are given the appropriate resources (including time) to ensure completion of the task.[40]

High-Risk Areas and Strategies for Improvement in Office Practice

Experience indicates that safety issues in the ambulatory setting differ from those in the inpatient setting in several ways. There are differences in the types of errors (treatment errors predominate in inpatient settings, whereas diagnostic errors do in outpatient settings), the provider–patient relationship (e.g., adherence is more critical in outpatient settings), organizational structure (ambulatory practices tend to lack the infrastructure and expertise to address quality and safety improvement), and regulatory and legislative requirements (there are required staffing ratios and accreditation requirements for hospitals, for instance, that do not exist for private practices).[41] In addition, the signal-to-noise ratio is much lower in outpatient settings: in ambulatory care, a physician may see 100 patients with lower abdominal or pelvic pain before seeing one with an acute adnexal torsion.

The outpatient setting also presents greater challenges for information transfer. Particularly in the case of patients with complex medical needs, the responsibility for care is often shared by multiple providers at many institutions. These clinicians may never meet, and they often use different medical record systems from one another. Such care has long, fragile feedback loops. In the hospital, if a patient has an adverse drug event, clinicians become aware of it very quickly; in the outpatient setting, a complication or missed diagnosis may not be identified for weeks or months, if ever.

Missed or delayed diagnoses are the most common problem leading to malpractice claims in the office gynecology setting, and test result interpretation and communication are common process breakdowns (see Table 29.5). As a starting point, office practices need to work on practical strategies for tracking and following up on test results to ensure that communication of these results to providers and patients is 100% reliable.[42] Tests revealing findings that are clinically significant but not critical (e.g., routine Pap smears, cervical cultures, initial prenatal profile) warrant particular attention. These nonemergency findings must be communicated appropriately to a responsible provider, who must acknowledge their receipt, and systems must be put in place to ensure that any requisite follow-up testing actually gets done.

In addition, explicit communication strategies and documentation of this communication (e.g., acknowledgment of receipt of communication) should be devised. There should also be clear escalation strategies (e.g., contact the head of the clinic or covering provider if the ordering physician is not available). Ordering providers must document the reasoning underlying their test orders and their contact information. Clear guidelines must be instituted to make sure that abnormal labs are appropriately communicated to someone who can take action.

There are potential technologic strategies for improving the result management process. Although some physicians are conscientious enough to invent their own mechanisms to solve the problems inherent in paper-based systems, the significant variability in the solutions highlights the weakness of this approach. A result management tool that is integrated with an electronic medical record system may improve the process of test result review. Designers of these systems may incorporate standardized features that easily allow physicians to focus their attention on abnormal test results, track all the tests they have ordered and ensure results are reviewed, and the system may warn physicians if patients have missed tests.[43]

It is important to realize that paper systems can also be successful, and that even hospitals and clinics unable to afford expensive technology can create systems that are effective and safe. Examples include log books or spreadsheets that are managed by centralized personnel within a clinic and track tests that are sent and results that return. Technology is helpful but can also introduce new errors, so it is essential that these processes, whether paper- or technology-based, be constantly assessed for potential failures.

Clear lines of responsibility for follow-up must be established to ensure that there are no misunderstandings. For example, if an endometrial biopsy is performed in the office, is the primary gynecologist or the gynecologist who actually performed the procedure or the pathologist or the primary care provider responsible for following up on the pathology? Such circumstances were noted in an office-based gynecology claim contained in CRICO/RMF's most recent CBS data analysis previously mentioned.[27]

A postmenopausal patient, with a 10-year history of using oral estrogen replacement therapy, presented to her primary gynecologist with complaints of vaginal bleeding. The patient had just completed a pelvic ultrasound ordered by her primary care provider, with the ultrasound showing a 16-mm endometrial stripe. The primary gynecologist asked the patient to return for an endometrial biopsy in the office. However, a gynecology physician colleague actually performed the patient's procedure because the primary gynecologist was

away on vacation. The pathology report was sent to the second gynecologist who forwarded the report to the primary gynecologist for follow-up. The pathology report was notable for "normal appearing but scant endometrial tissue," with the notation, "insufficient tissue for diagnosis." The primary gynecologist reviewed the dictated note of the office procedure and negative biopsy but did not review the actual pathology report. An office nurse contacted the patient, reassuring her that the endometrial biopsy was negative. It was unclear as to who had asked the nurse to contact the patient about her biopsy results. The primary care provider never received a copy of the pathology report. Two years later, the patient returned to her primary gynecologist with complaints of vaginal bleeding. An endometrial biopsy was immediately performed and the pathology notable for adenocarcinoma of the uterus. Although she had aggressive treatment, she passed away 3 years later from complications related to her advanced disease. A claim was asserted against the doctors, alleging delayed diagnosis of her condition contributed to the patient's premature death. The case ultimately settled for the patient and her estate in excess of 1 million dollars.

This case highlights the importance of having explicit policies and procedures for communicating critical test results between providers, documenting provider to provider communication, and establishing who has primary responsibility for follow-up. Referrals to other providers need to have similar tracking mechanisms to ensure that referrals are completed and the information comes back to the referring physician.

In addition to test result and referral tracking, cognitive errors related to missed and delayed diagnosis need to be addressed, just as errors in judgment, vigilance, and memory do. These cognitive errors were universally found in one study of missed and delayed diagnosis.[26] The types of cognitive errors that physicians make have been well studied,[44–46] and several examples are listed in Table 29.10.

TABLE 29.10 Common Cognitive Pitfalls

Oversimplification of causality	Application of past events leads to underestimation of future consequences
Thinking in causal series	The tendency for individuals within complex systems to think in linear sequences to form an immediate action without being aware of the "side effects" of that action to the system as a whole
Availability bias	The tendency to assume when judging possibilities or predicting outcomes—that the first possibility is selected as the most likely possibility—*acts as a cognitive* "short cut" *in the setting of a complex situation*
Confirmation bias	The tendency to focus on evidence that supports a working hypothesis without looking for further information that may refute the original hypothesis
Overconfidence bias	The tendency to believe we know more than we do
Order effects	The tendency to remember the beginning or end of information but not all the information required during information transfer

Some strategies for mitigating cognitive errors include reducing reliance on memory (e.g., using computerized order entry systems to detect drug–drug interactions) and forcing consideration of alternative diagnostic plans or second opinions (e.g., requiring chart audits of patients presenting with breast complaints to ensure the workup is complete). Clinical decision support systems have great promise, particularly in the ability to ensure that guideline recommendations are available in the workflow at the point of care.

Medication safety is probably the most studied topic in outpatient safety research. One study found that adverse drug events occurred in 25% of primary care patients and that 11% of these events were preventable.[47] Solutions such as electronic prescribing have been advocated, and now national incentives exist for their adoption. Electronic prescribing systems can help prevent drug–drug interactions of drug-allergy interactions. However, there is still much to learn about the effects of e-prescribing systems on errors and how they can be optimized. For example, a better understanding is needed of how to provide clinically important decision support without causing unnecessary disruptions in clinicians' workflow and how to maintain accurate medication lists in electronic medical records.

Nationally, there is a strong interest in reducing preventable hospital readmissions and this has focused attention on the flow of information during the transition of care from the hospital to other settings. The concept of "no dropped balls" has an inherent appeal, but it requires teamwork among clinicians in these various settings. Providers seeing patients for their outpatient management or follow-up should always be provided with postdischarge medication changes, follow-up plans and appointments, pending tests, and the details of advance care planning—yet we know that such information is not always transmitted. For instance, 41% of patients have tests whose results are pending at the time of hospital discharge, and often, neither the discharging physician nor the primary care provider is informed about the test results.[48] Clear lines of responsibility need to be created to determine who will follow up on which result before the patient is discharged. In addition, the discharging hospitals need to implement high-quality discharge summaries that are transmitted in a reliable way, whereas outpatient physicians' offices need to provide access to timely postdischarge visits and allow time for review of the discharge materials, reconcile medications, discuss symptoms, and perform appropriate follow-up.

In the pay-for-performance era, robust safety-related metrics may help to improve the safety of ambulatory care. Potential examples of such metrics include the percentage of medication lists that accurately reflect what the patient is actually taking or the percentage of abnormal Pap tests or breast lumps for which appropriate follow-up has been performed. In 2005, the Ambulatory Care Quality Alliance recommended preventive clinical performance measures for gynecologic ambulatory care that include the percentage of women having had mammograms or Pap tests during the measurement year or in the previous 2 years.[49] Unfortunately, as the College recently noted, there is a lack of consensus on what national performance measures should contain and what areas they should target.[50] What is clear is that all metrics should link in a meaningful way to outcomes. The College does provide examples of quality outcome indicators for obstetrics and gynecology, most of which involve hospital-based care.[50] Of the 16 outcome indicators pertaining to gynecologic care, 4 are potentially applicable to office-based surgery (Table 29.11).

Further work needs to be done to define appropriate measures and create better systems for capturing this kind of data.

A summary of ambulatory safety focus areas, issues, and strategies for improving office practice is provided in Table 29.12.

TABLE 29.12 Ambulatory Safety Focus Areas

Focus Area	Issues	Strategies
Missed and delayed diagnosis	Test result follow-up	Result tracking systems Escalation Clear lines of accountability
	Referral follow-up	Referral tracking systems
	Cognitive errors	Decision support
Medications	Medication list accuracy	Medication reconciliation tools
	Medication errors	E-prescribing
Transitions of care/preventing readmissions	Communication of clinical information across the continuum	Improved discharge processes
Procedural safety	Anesthesia Technical issues	Checklists/protocols Simulation Credentialing
	Incorrect procedure Informed consent Emergency response	Timeouts Checklists/protocols Drills

Creating a Safe Environment for Office-Based Procedures and Practice

The College's report released in 2010 on patient safety in the office featured a number of activities and procedures that any office practice could implement and customize as needed to create a safe environment for patient care.[32] The primary focus of this report was to provide information and tools for safely introducing invasive technologies in the office setting. The report maintains that efforts required to implement these activities can increase the efficiency of office practice, reduce expenses related to error recovery and correction, and improve patient satisfaction. As noted previously, the foundation of office safety is based on principles of effective communication, staff competency, safe medication practice, accurate patient tracking mechanisms, general procedural safety, and anesthesia safety (Table 29.13).

Office safety requires leadership. In office settings where outpatient surgery procedures are done, a specific person should be designated to serve as the medical director. The medical director assumes primary responsibility for ensuring safe practice of such procedures, verifying the qualifications and safety of staff, equipment, space, and supplies. The medical director serves as a champion and role model for effective team practice, helping to coordinate teamwork among all members of the office staff. In a solo practice, the physician serves as the medical director. However, in larger practice settings, the medical director can be a physician partner or other designated individual such as a nurse supervisor who is tasked with ensuring quality and patient safety in office practice.

Tools recommended by the College to facilitate safe practice in the office include checklists, safety drills, and having policy and procedure manuals that address

TABLE 29.11 Example Outpatient Gynecologic Clinical Outcome Indicators

1. Ambulatory surgery patient admitted or retained for complication of surgery or anesthesia
2. Unplanned removal, injury, or repair of organ during operative procedure
3. Discrepancy between preoperative diagnosis and postoperative tissue report
4. Delay or missed initiation of antibiotics prior to surgical procedure

Adapted from Women's Health Care Physicians, Committee on Patient Safety and Quality Improvement. *Quality and Safety in Women's Health Care*. 2nd ed. Washington, DC: American College of Obstetricians and Gynecologists; 2010.

TABLE 29.13 Foundation of Office Procedural Safety

Major Elements in the Foundation of Office Procedural Safety

- Effective communication
- Staff competency
- Safe medication practice
- Accurate patient tracking mechanisms
- General procedural safety
- Anesthesia safety

Modified from American College of Obstetricians and Gynecologists. Report of the Presidential Task Force on Patient Safety in the Office Setting. *Presidential Task Force on Patient Safety in the Office Setting (2008–2009)*. Washington, DC: American College of Obstetricians and Gynecologists; 2010.

credentialing and privileging; informed consent; patient rights; timeouts; and emergency response to critical, unexpected events such as excessive sedation (Table 29.14).

Checklists have long been used in nonmedical industries such as aviation, serving as cognitive aids to assist users through a series of steps toward accurate task completion.[51,52] Checklists in aviation date back to the 1920s and have been shown to reduce the frequency of error and prevent mistakes.[53] The use of checklists has infiltrated into the health care arena and has also been found to reduce the frequency of error and avert mistakes.[54-56] The College provides examples of checklists ranging from daily office set up to office surgery safety.[32]

Their office surgery safety checklist includes the following:

- Patient identifiers
- Confirmation of pertinent patient issues prior to use of anesthesia/analgesia
- Antibiotics immediately prior to incision
- Intraoperative use of medications, sedation, and fluids
- Postoperative instrument and sponge counts
- Specimen verification
- Checks for equipment-related issues and other key issues
- Patient care issues to consider prior to discharge

It is important to keep in mind that using checklists does not guarantee all errors will be prevented. Degani and Wiener[53] conclude from their research on checklists in aviation that humans remain at the center of task completion, and the unique interaction between humans, devices, checklists and their environment must be kept in mind in the design and successful use of checklists.

The College offers a practical seven-step blueprint, applicable to offices of all sizes, for making office practice safer (Table 29.15).

The College does not position this blueprint, their checklists, and other tools as a standard for patient safety in the office setting. However, they do support these endeavors as a means by which to heighten provider awareness about the importance of establishing a safety culture in the office and incorporating patient safety in all aspects of office-based care.

TABLE 29.14 Tools Facilitating Safe Office Procedural Practice

Tools Facilitating Safe Office Practice—Examples Not Limited to the Following
• Checklists
◦ Office setup
◦ Preoperative
◦ Intraoperative
◦ Postoperative
◦ Office surgical safety
• Safety drills
◦ Vasovagal episode
◦ Reaction to local anesthetic
◦ Cardiorespiratory arrest
◦ Uterine hemorrhage
◦ Excessive sedation
• Policy and procedure manual(s)
◦ Credentialing and privileging
◦ Informed consent
◦ Patient rights
◦ Infection control
◦ Timeouts
◦ Emergency response
◦ Excessive sedation
▪ Cardiorespiratory arrest
▪ Environmental accident
▪ Fire
◦ Procedure outcome reporting
◦ Adverse event and near-miss reporting

Modified from American College of Obstetricians and Gynecologists. Report of the Presidential Task Force on Patient Safety in the Office Setting. *Presidential Task Force on Patient Safety in the Office Setting (2008–2009)*. Washington, DC: American College of Obstetricians and Gynecologists; 2010.

TABLE 29.15 Starter Steps to Office Procedural Safety

Seven Starter Steps to Office Procedural Safety
1. Designate a medical director with specific patient safety responsibilities
2. Create a training manual for all office staff
3. Create and perform a safety drill (can be quarterly, including one for CPR)
4. Create a checklist for one procedure and follow it, revising it as needed
5. Survey and certify staff—basic or advanced cardiac life support training
6. Carefully re-examine anesthesia and analgesia methods and compare with published guidelines
7. Discuss patient safety goals with each patient to create a safer environment for the procedure

CPR, cardiopulmonary resuscitation.

Modified from American College of Obstetricians and Gynecologists. Report of the Presidential Task Force on Patient Safety in the Office Setting. *Presidential Task Force on Patient Safety in the Office Setting (2008–2009)*. Washington, DC: American College of Obstetricians and Gynecologists; 2010.

CONCLUSIONS

Ambulatory safety in the office gynecology or office-based procedural settings is a critical issue. Malpractice experience provides a view into some of the main risk areas, such as missed and delayed diagnosis. However, better mechanisms to identify and measure problem areas are needed. It is essential to develop an ambulatory safety culture and infrastructure to analyze events and improve processes, and this requires strong leadership. Providers and administrators in offices and procedural settings need to develop expertise in analyzing events from a systems perspective and in developing and implementing process redesign solutions (e.g., standardization, simplification, checklists) in order to minimize risks to patients. The role of leadership in guiding office staff members to strive for excellence in the provision of safe patient care cannot be underestimated. All physicians, whether practicing solo or in small group to large multispecialty office settings, can lead by example and make patient safety their highest priority.

CLINICAL NOTES

- Of the estimated 902 million visits made to office-based physicians during 2006, visits to obstetrician-gynecologists comprised about 8% of them.
- The practice of obstetrics and gynecology will become increasingly focused on managing health care needs of an older population as the average lifespan increases and the baby-boom population ages.
- A review conducted during 2007 by the CRICO/RMF found that 623 office-based malpractice cases comprised 27% of total malpractice cases alleged across all medical and surgical specialties between 1997 and 2006. The major clinical conditions identified in the claims were cancer, infection, myocardial infarction, benign tumor, or stroke.
- In a 2007 review, missed or delayed diagnosis of a clinical condition was alleged in 324 (52%) office-based malpractice cases. Failure or delay in ordering a diagnostic laboratory test was alleged in 62%; 56% alleged poor follow-up of a plan and, if indicated, a referral; and 14% involved medication errors.
- Missed or delayed diagnoses are the most common problem leading to malpractice claims in the office gynecology setting, and test result interpretation and communication are common process breakdowns.
- A safety culture acknowledges the high-risk, error-prone nature of an organization's activities; provides a blame-free environment where individuals are able to report errors or close calls without punishment; recognizes that most errors are from good people working in bad systems ("not bad apples"); and demonstrates organizational willingness to direct resources to address safety concerns.
- There are tools specifically designed to assess safety culture in the office setting, identifying how staff members perceive their environment and shedding light on specific areas in need of improvement.
- To achieve a culture of safety, leadership support is essential because leaders, whether in the office, the outpatient surgery facility, or the hospital, set the tone for acceptable behaviors and actions in the workplace.
- Compiling errors is useful only if the results are to improve system safety. Office practices need to develop skills in analyzing events, understanding root causes, and designing and implementing system improvements.
- Experience indicates that safety issues in the ambulatory setting differ from those in the inpatient setting in several ways. There are differences in the types of errors (treatment errors predominate in inpatient settings, whereas diagnostic errors do in outpatient settings), the provider–patient relationship (e.g., adherence is more critical in outpatient settings), organizational structure (ambulatory practices tend to lack the infrastructure and expertise to address quality and safety improvement), and regulatory and legislative requirements (there are required staffing ratios and accreditation requirements for hospitals, for instance, that do not exist for private practices).
- The foundation of office safety is based on principles of effective communication, staff competency, safe medication practice, accurate patient tracking mechanisms, general procedural safety, and anesthesia safety.
- Tools to facilitate safe practice in the office include checklists, safety drills, and having policy and procedure manuals that address credentialing and privileging; informed consent; patient rights; timeouts; and emergency response to critical, unexpected events such as excessive sedation.

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CHAPTER 30

Medical-Legal Issues in Office Gynecology

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The practice of medicine in general, and obstetrics and gynecology in particular, takes place in a professional liability environment that is increasingly difficult for physicians to navigate. Obstetrician-gynecologists face a constant risk of contributing to or even committing medical errors, or of being sued for allegedly committing malpractice, for actions in all of the environments they work in: the operating room, on rounds in the hospital, attending patients in labor and delivery, or while seeing patients in the office. Although each of these practice environments pose unique risks, the physician's office is generally the fulcrum around which actions in the other two arenas pivot.

This chapter concerns itself with the major liability risks for physicians practicing gynecology in the office. As such, most liability risks for obstetrical care will not be discussed, although some of the topics do concern similar areas in office-based obstetrical care, for example, liability issues for screening for genetic disease. Similarly, a discussion of *all* of the potential ways in which a practicing obstetrician-gynecologist might be sued for actions or failures to act in the office is beyond the scope of this chapter, although there are comprehensive reviews of medical malpractice issues available.[1]

The practice of medicine, the law of medical malpractice, the business of medicine, and the regulation of the medical profession by the federal government as well as the individual states are all constantly evolving but not in lock-step fashion. In some instances, advances in medicine outstrip the willingness of most or all state legislatures or of Congress to intervene, for example, issues related to assisted reproductive technology. In other areas, such as abortion, both the federal government[2] and the individual states may interfere with the individual physician–patient relationship in an arbitrary and/or particularly heavy-handed manner, as witnessed by (a) the U.S. Supreme Court's decision in *Gonzales v Carhart*,[3] which upheld the constitutionality of the Federal Partial Birth Abortion Ban Act of 2003, and (b) recent individual state efforts at compelled free speech for physicians[4] that requires them to provide specific information, some of which is medically incorrect, to women seeking abortion.[5] In both of these cases, there is a direct impact of federal and/or state law on what a practicing gynecologist cannot do, or must do, in the office or ambulatory setting.

Along with this existing spectrum of interference or noninterference is the added layer of ongoing and upcoming changes in information technologies and governmental micromanagement of medical decision making. Examples include the use of the Internet to communicate with patients, issues of electronic medical records, and the growing practice of telemedicine. Both individual states and the federal government have initiatives for these new developments; such incentives or mandates generally appear or are advanced under the umbrella of improved transparency of health information for patients, patient safety, or delivery of more efficient and less costly medical care. In general, all of these initiatives are in their infancy but certain to assume increasing importance in office gynecology practice. All of them are already broadly creating potential liability for practitioners in the office setting despite the fact that for the most part, they are poorly regulated (if they are regulated at all). Lastly, there is the new federal emphasis on clinical practice guidelines as a means of minimizing regional differences in practice patterns,[6] improve patient safety and quality of care, and the establishment of a more "evidence-based" approach to patient care.

GENERAL MEDICAL MALPRACTICE RISK IN THE OFFICE SETTING

Confidentiality of Information: Health Insurance Portability and Accountability Act and Other Requirements

The physician's medical office is first and foremost a storehouse of private, and often intimate, information about patients. The Health Insurance Portability and Accountability Act of 1996 (HIPAA)[7] is generally considered to be the enabling statute that protects the privacy of patient information. For most physicians and patients, HIPAA is little more than a lengthy series of forms, which patients rarely read, do not fully understand, and have to fill out almost every time they visit the physician's office. Most physicians, patients, and health policy experts also believe that HIPAA's "privacy rule"

protects medical confidentiality and likely assume that the confidential information contained in the medical record is *protected* from access by HIPAA. This may have been the legislative intent of the bill, but the reality of HIPAA is that its protection of confidential medical information is considerably less than both patients and physicians think it is. HIPAA is also a *disclosure* act that provides unanticipated and unwelcome access to patient information by a plethora of health care–related institutions and individuals.[8] Physicians in the office, as well as their patients, need to be aware of this: "Effective in April 2003, the federal government gave six hundred thousand 'covered entities'—such as health care plans, clearing houses, and health maintenance organizations—regulatory permission to use or disclose protected information for treatment, payment, and health care operations (known as TPO) without patient consent."[8] The HIPAA rules also permit physicians, nurses, and other health care professionals to disclose protected patient information for treatment purposes without patient authorization. For example, the privacy rule includes a proviso, which allows breach of confidentiality of patient records when the health or safety of third parties is threatened.[9]

Although a discussion of the complexities of HIPAA is well beyond the scope of this chapter, there are several take-home messages which all physicians practicing office gynecology need to communicate to their staff. First, the record-keeping requirements and forms mandated by HIPAA must be complied with to the letter, regardless of how senseless or inefficient the entire paperwork process might appear. Second, all office staff who deal with patient records and insurance matters should be knowledgeable about HIPAA basics so that they can accurately—and in an uncomplicated manner—answer questions patients may have about who might access their medical information and under what circumstances such information might be released even if they do not consent.

The degrees of separation among the widely differing institutions HIPAA regulations apply to are surprisingly narrower than both patients and physicians might think. For example, HIPAA could easily allow an insurer to give data to a bank it owns in order to deny a physician's patient a loan. The structure of HIPAA allows the creation of paths of information without audit trails which, along with the relative lack of U.S. Department of Health and Human Services (HHS) enforcement and penalties (at the time of this writing, violations of HIPAA have no apparent negative consequences), arguably creates situations, which increase the probability that information might be misused. Despite this, all relevant physician office forms should clearly and legibly indicate that the physician, his or her office personnel, and practice *cannot* be held responsible for what insurance carriers do with the private patient information they, by law, have access to.

There is little evidence to suggest that the move to electronic medical records will make the risks of unwanted disclosure of private patient information any better. Despite numerous calls from some members of the legal profession that the push for electronic medical records is moving forward without adequate provision for the protection of patient information in electronic health records,[10] legislation with adequate consent provisions or protections is still inadequate at best.

For those physicians and/or medical groups conducting or participating in active clinical trials, HIPAA has had a distinctly negative impact on the conduct of human subjects health research.[11] A perusal of any of the subspecialty journals over the past decade will demonstrate a marked decrease in the number of well-done, retrospective surgical studies, which are valuable in guiding clinicians in difficult management decisions. The American Congress of Obstetricians and Gynecologists (hereafter ACOG) has recognized these unanticipated negative effects of HIPAA and recently published a guidance document, HIPAA in Practice, Research Under the HIPAA Privacy Rule, which outlines how HIPAA privacy rules will affect office gynecology practitioners and practices whether they are actively involved in clinical investigations or not. The American Medical Association also has a user-friendly and highly informative webpage, which addresses frequently asked questions about the HIPAA privacy rules.[12]

Physician Conduct in the Office—Basic Do's and Don'ts

Physician conduct in the office should be professional at all times. Some of the simpler ways to avoid liability in the office gynecology setting are self-evident: accurate and timely record keeping, preservation of patient confidentiality (particularly if office phone conversations can be overheard by other patients), compliance with HIPAA disclosure requirements, having an educated staff who treats patients with respect and courtesy regardless of whether they are interacting with them on the phone or in person, and professional conduct by all health practitioners in the office. Implicit in the latter is avoidance of inappropriate verbal remarks or physical contact with patients; ACOG has highlighted the importance of this in its August 2007 Committee Opinion on Sexual Misconduct: "Sexual contact or a romantic relationship between a physician and a current patient is always unethical, and sexual contact or a romantic relationship between a physician and a former patient also may be unethical."[13] One corollary of this code of conduct is that examinations of patients should be performed only with the necessary amount of physical contact required to obtain a diagnosis and effect treatment, and accompanied by appropriate explanation as well as by a chaperone. Similarly, those clinicians who have medical students or resident house staff working

with them in the office must be sure that the same caveats apply to the interactions of these individuals with patients. Just as patient informed consent is required ahead of time for medical students examination of patients under anesthesia,[14] similar conduct is required for contact between students and patients and/or house staff and patients in the office.

Knowing the Standard of Care and Keeping Up With Literature/Certification

ACOG maintains an extensive array of educational materials on their website that member physicians can access. Maintenance of annual board recertification is strongly recommended (at some institutions it is a requirement) for those physicians who were not "grandfathered" in before 1985, and voluntary recertification for those whom annual recertification is not a requirement has been encouraged for years. It is important that physicians in active clinical practice of office gynecology keep up with the relevant peer-review medical literature in the specialty as well as current recommendations for clinical practice by ACOG.

Physician certification and recertification has become increasingly important in the patient safety/quality of care movement.[15] Maintenance of board certification may be a requirement for obtaining a state medical license, obtaining hospital privileges, or being added to a list of providers for insurance companies or a health maintenance organization. The promotion of board certification has been advanced as one of the integral components of a "systems" solution to the problem of medical errors by physicians.[16] Lack of board certification, ignorance of what the recommended (and published) standard of care is for medical professional societies such as ACOG, and failure to keep up on the current medical literature are all items which may create difficulties when physicians are involved in malpractice litigation, both during deposition by plaintiffs' counsel as well as during trial.

At the present time, board certification is regulated by the medical profession itself through medical specialty boards. Most medical professional organizations publish medical journals, which frequently contain statements about recommended clinical guidelines. These guidelines, which purport to assist with patient management decisions based on the best available evidence, are not binding on physicians nor necessarily considered the gold standard of care by juries in a medical malpractice trial. However, physicians need to be aware of them, and if their practice differs significantly from commonly accepted guidelines, they should be prepared to provide some evidentiary basis to support their decision-making process(es) should the need arise.

The recently publicized data demonstrating significant individual variations in clinical practice, as well as differences in patient use of medical–surgical services throughout the United States, and the increasing emphasis on cost control and patient safety have created pressure for more uniformity in physician practices. This has created a situation where medical professional practice guidelines may become politicized[17] and where individual state legislatures, as well as the federal government, may be tempted to insert themselves more frequently into the physician–patient relationship by legislating standards of care independent of what the medical profession views as the best practice(s) supported by the best evidence.[18] This transformation of clinical practice guidelines into legislative mandates has thus far been confined mostly to narrow areas, such as abortion and dealing with communicable diseases. Further intrusion by the government into what physicians cannot do, or must do, will inevitably enter dangerous territory[19] when the law specifies how additional types of medical care must be delivered. This will be true even at the office practice level where a "cookie-cutter" algorithmic approach may not take into adequate account individual patient circumstances which might suggest or dictate a clinical management approach at odds with that felt to be the "best practice" by the government.

The bottom line for physicians in this certain-to-be evolving area is that physicians must be aware of what the medical jurisprudence requirements are in the state or states they practice in. Physicians and medical staff must also be aware of what conduct is required in certain clinical situations, such as reporting requirements for communicable diseases or when faced with a patient who may have been a victim of domestic violence.

Conflicts of Interest—Informing Patients of Business and Industry Ties

Because the practice of medicine has become more of a business and industry-sponsored clinical trials have moved from the confines of large academic medical centers into the general medical community, physician-investigator ties to the medical device and pharmaceutical industries have deepened. In addition, some physicians have become more entrepreneurial in their business and medical endeavors. Both of these developments have raised the specter of potential conflicts of interest between the physician's primary fiduciary duty to his or her patient and the demands or pressures for clinical testing and reimbursement for innovative therapies or devices the physician or physicians' medical group may have a financial interest in.

ACOG and numerous other professional societies have published clear guidelines on commercial enterprises in medical practice.[20] These guidelines attempt to delineate the scope of business/industry activities which are/are not permissible. The list of such activities is long and the language is problematic at the very least. For example, "[t]he following activities are considered unethical . . . sale or promotion of nonprescription

medicine, sale or promotion of presumptively therapeutic agents that are generally not accepted as part of standard medical practice."[20] Under a plain-language reading of these ACOG guidelines, it would appear that recommending a dietary supplement to a patient for treatment of menopausal symptoms is unethical behavior because such herbal remedies or treatments are not U.S. Food and Drug Administration (FDA)-approved, have not undergone rigorous clinical testing, and are generally not considered to be part of the "standard" practice of medicine. Similarly, it would appear that medical practices that advocate, perform, and bill for "alternative" but not universally accepted forms of treatment or therapy (e.g., acupuncture for treatment of a variety of benign conditions) are also engaging in unethical behavior.

It is not clear what the legal ramifications of ACOG's Committee Opinion are, or what potential liability issues it raises for physicians; from a legal point of view, the ACOG Committee Opinions are not binding and may be viewed as either simply just a general recommendation or advice. These gray areas notwithstanding, some of the recommendations—such as a prohibition against the sale or promotion of any product in whose sale the physician has a significant financial interest in[20]—would appear to be self-evident and not controversial.

What is clear from the current medical and legal literature is that patients have now rightfully come to expect that treating physicians and physician-investigators be transparent about their vested financial interests in any medical or surgical therapies/devices they are recommending. This holds true in the traditional practice as well as the clinical research setting.[21] Requiring the routine disclosure of such information does not appear to have an adverse effect on patient willingness to go forward with the recommended drug therapy or medical device, but lack of transparency does seems to create problems, particularly in retrospect when untoward events occur.[22]

There is no law or rule as to the precise limits of information physicians with potential financial conflicts of interest must reveal. At present, no one expects physicians to delineate their investment portfolio or what drug or medical device companies they own stock in, and no current or proposed state or federal legislation yet requires this, but a significant financial interest in an innovative new medical device or type of surgical equipment, or ownership interest in a company manufacturing medical products being tested or promoted in the office clearly qualifies for disclosure to patients.

Ethics and Informed Consent for Standard and "Innovative" Therapies

The realm of "innovative" medical practice lies between standard or traditional office medical practice that focuses the physician's attention exclusively on the well-being of the individual patient, and the structured clinical trial in which an office patient is enrolled in an organized investigation of a particular treatment that is designed to produce generalized knowledge rather than provide direct benefit to a specific patient. What constitutes innovative medical practice, however, is not precisely defined in either the medical or legal literature and thus occupies a legal and regulatory "gray area" between standard therapy and organized clinical research. As such, it also represents a real but ill-defined area of potentially increased medical liability exposure for physicians.[23]

Innovative therapy can be surgical or medical in nature, and although it is often thought of as an activity which goes on in the operating room, it could easily apply to alternative medical therapies which physicians employ in the office, or to "experimental" or non–FDA-approved medical therapy for a gravely ill patient.

Standard medical practice is generally governed by medical profession guidelines and individual state medical boards, and clinical investigations or trials are generally reviewed and monitored by local/hospital institutional review boards (IRBs) with oversight provided (depending on funding) by the FDA and the Office of Human Research Protections (OHRP) of the HHS.[24] Despite both state and federal involvement in the areas of clinical investigations or trials, the issue of patient access to unapproved medical therapy has been heavily litigated. Efforts by patients and their advocates to establish a constitutional "right" to unapproved but potentially life-saving medical therapy have been firmly rejected by federal Appellate courts[25] as well as the U.S. Supreme Court.[26]

There is no formal oversight of innovative medical or surgical practice in the office setting and no consensus in the medical literature on the precise boundaries between innovative therapy and outright experimentation. One of the few studies[27] examined, senior, predominately male surgeons' attitudes toward innovative surgery and how it should be regulated and had several interesting findings: (a) "planned experimental surgery" was more likely to be classified as surgical research, whereas "introducing small novelty modifications during a standard operation" was most often considered routine clinical practice[27]; (b) the intent of the surgeon was the dispositive factor; that is, spontaneity would signify routine care, whereas premeditation was the hallmark of clinical research; and (c) the greater the degree of variation from the standard of care the more likely the intervention would be considered both experimental and research.

Of course, one reason why such practice is a gray area is because such intervention may be intended to both benefit the individual patient *and* to generate generalizable knowledge applicable to similarly situated patients. More importantly, the aforementioned

study demonstrated that almost two-thirds of the participating surgeons were unfamiliar with federal oversight of clinical research through OHRP despite their acknowledgment that specific informed consent *is* required for planned innovative activity. One firm conclusion which may be drawn from the study is that more oversight of innovative medical and surgical therapy practice is needed because many of the innovative practices, which go on in the operating room as well as in physicians' offices, are below the regulatory radar screen.

Informed consent must always be obtained from a patient before standard medical therapy is undertaken. Although consent is implied in a general physical examination or evaluation and patient's need not sign consent forms before a physical examination, specific informed consent is generally required before invasive office procedures such as colposcopy or endometrial biopsy. Similarly, patients may sign specific informed consent forms for planned inpatient or outpatient surgical procedures in the office or hospital setting, and if participating in a clinical trial (e.g., drug study), there are invariably extensive materials which must be read by and reviewed with the patient prior to their agreeing to participate.

The take-home point from the medical and legal literature appears to be that planned deviations from standard office medical or surgical practice require informed consent specific to those planned interventions so that patients can be appraised of their treatment options as well as the unique potential risks (and benefits) innovative therapy holds. ACOG has also advocated this approach[28] and cautions physicians to (a) employ innovative procedures only when they have achieved sufficient training to be skillful and (b) to avoid adopting innovative procedures and practices on the basis of advertising and promotion by industry.

Physicians engaging in innovative or nonstandard medical or surgical practice in the office must understand that from a liability point of view, they are on their own: the "learned intermediary" doctrine[29] provides a fairly robust shield for manufacturers in this context, and the overwhelming bulk of medical-legal liability is going to fall on the treating physician(s) should untoward events arise. The learned intermediary doctrine provides that manufacturers of prescription drugs and medical devices discharge their duty of care to patients by providing warnings to the prescribing physicians. The justification for this doctrine is grounded in the fact that consumers cannot buy prescription drugs or devices directly; they must consult with and receive the approval of a physician. By providing adequate warnings to a prescribing physician, who in turn provides appropriate patient-specific warnings, the manufacturer discharges its warning responsibilities. The prescribing physician acts as a "learned intermediary" between manufacturer and consumer and has the primary responsibility of warning patients of the hazards of prescribed pharmaceutical products or devices.

Refusal to Provide Treatment or Counseling: "Conscience" Claims

Once a patient and his or her physician have voluntarily entered into a treatment or care relationship,[30] the relationship may be terminated by mutual consent for any one of a number of legitimate reasons; for example, the physician and patient cannot agree on treatment goals, or personality conflicts make the situation uncomfortable or too difficult.[30] A patient may unilaterally terminate a physician–patient relationship for *any* reason.[30] However, physicians do not have the same flexibility and are duty-bound to continue to treat a patient once treatment has begun except under carefully defined circumstances.[30] Both federal and state law place limits on required physician conduct,[30] although both allow termination of patient treatment for reasons of conscience under certain circumstances. When a physician does unilaterally terminate a treatment relationship with a patient for reasons of conscience, it is usually for religious reasons, although a matter of conscience need not be religious in nature.

Specific care sought by patients, which is more likely to create conflict with a physician's personal beliefs, is common in the office gynecology setting. These include the provision of contraception (particularly emergency contraception) and performing or counseling regarding abortion or abortion-related services.[31] Physicians are generally permitted to refuse to provide emergency contraception to patients, counsel regarding abortion-related services, or to perform abortions if it conflicts with their religious or personal moral beliefs. Largely, as a result of the abortion wars of the past two decades, more than 45 states have "conscience clauses" on their books, which attempt to "balance a physician's conscientious objection to performing an abortion with the profession's obligation to afford all patients nondiscriminatory access to services."[32]

Physician refusals to provide reproductive medicine–related services in the office for moral reasons are common enough to be recognized and protected by laws in several states; for example, Texas.[33] Both the American Medical Association[34] and the American Congress of Obstetricians and Gynecologists (ACOG)[35] support the concept of physician conscience claims as a reason to refuse provision of certain medical services, and both organizations have stated that physician refusal to treat in such circumstances is both legal and ethical. Additional support for physician conscience claims can be found in recent surveys, which have looked at the issue of religion, conscience, and controversial clinical practices. The few clinical studies of this activity have generally found that the majority of physicians (63%) believe that it

is ethically permissible to explain their moral objections to patients. Just as important is the finding that an even higher percentage (86%) also believed that physicians are obligated to present all therapeutic options as well as provide alternate providers who might help the patient,[36] an action which is not required under current federal and most state laws.

Physician refusal to provide certain medical services or counseling thus rests on firm medical ethical grounds. There is further statutory protection offered to such conduct under individual state conscience clause legislation, and the First Amendment to the Bill of Rights of the U.S. Constitution,[37] which protects actions guided by sincerely healed religious beliefs. There *are* limits to such protection, however. A physician's or physician group's constitutional right to free exercise of religion does not exempt them from providing services when such refusal interferes with their obeying state laws which prohibit discrimination based on sexual orientation. Although there is little medical case law in this area, the recent California Supreme Court case of *Guadalupe T. Benitez v North Coast Women's Care Medical Group, et al.*[38] determined that a physician does not have a constitutional right to refuse to perform intrauterine insemination (or other medical services) for religious reasons on an established patient merely because they were unmarried and gay when there are state laws specifically prohibiting discrimination in the provision of medical services against individuals simply because of their sexual orientation. Although discrimination against an individual based on sex or gender is not protected conduct, the Court did not resolve whether a physician could refuse to provide artificial insemination for a patient simply because they were not married; it would appear that marriage is not a "protected" class from physician denial of medical care, at least until there is litigation establishing this.

Clinicians also need to be aware that conscience clauses may also operate against them. The central role of pharmacists in providing birth control and emergency contraception, and the ready availability of conscience clauses for pharmacy professionals, have created a situation where clinicians practicing office gynecology may find themselves writing prescriptions for patients, either for routine birth control or emergency contraception, which patients cannot fill because local pharmacies either refuse to carry such medications or because pharmacists refuse to fill them.[39] Admittedly, this is less of a problem for emergency contraception because FDA approved some emergency contraceptives for over-the-counter status for women age 17 years or older, but the situation is still potentially a problem for patients and providers.

Pharmacists may refuse to fill a legitimate patient prescription for birth control pills or emergency contraception on conscience grounds. During the past 10 years, this practice has spread to many states but pharmacists' conscience claims for refusing to fill a prescription for contraceptives remains highly controversial.[40] At present, there does not appear to be a quick fix for this potential conflict between the conscience of a physician or pharmacist and a legitimate medical need for a patient, particularly for physicians practicing office gynecology in rural settings with few choices among pharmacists and patient populations with limited financial resources who may not be able to afford to order such medications via the Internet. One proposed solution suggests either a required physician notice or referral policy by pharmacists,[41] but it is not unreasonable to expect that many pharmacists who refuse to dispense emergency contraception for conscience reasons may also refuse to refer patients to a pharmacist who will. Telemedicine may offer a potential solution for some patients who have Internet access if they have a willing pharmacist and can access a more distant physician willing to provide contraceptives or abortion drugs.[42]

SPECIFIC NEW LIABILITY RISKS IN OFFICE GYNECOLOGY

Appropriate Screening for Breast Cancer

One of the most common medical malpractice lawsuits currently being brought against obstetrician-gynecologists is the failure to diagnose breast cancer in premenopausal women. A recent controversy about breast cancer screening was prompted by the publication of the HHS U.S. Preventive Services Task Force's (hereafter USPSTF) revision on screening for breast cancer, particularly for premenopausal women. In 2009, a panel of scientists selected by HHS to serve on the USPSTF made three specific breast cancer screening recommendations:

1. Routine mammography screening for women in their 40s was not warranted because the absolute benefit from routine mammography screening of women in their 40s was deemed to be too low to offset the "harms" of unnecessary surgical evaluation.
2. Mammograms for women age 50 years or older should be done every 2 years, not annually.
3. Mammograms should not be performed after the age of 74 years, because there is insufficient data to demonstrate that they were of benefit in women that age or older.[43]

The first recommendation was made despite the fact that breast cancer is one of the leading causes of death for women in their 40s, and there is an abundance of data demonstrating that routine mammographic screening of women significantly reduces the breast cancer death rate in this age group. In fact, this recommendation represented an about-face from established practice of beginning routine annual screening of premenopausal women for breast cancer starting at age 40 years (in the absence of strong family history which might warrant annual screening starting at an even younger age).

Sharp criticism of the new federal government regulations was not just restricted to the public or politicians eager to demonstrate their commitments to women's health; the new mammography screening recommendations did not sit well with the breast cancer community[44] or numerous specialty medical societies.[45] Opponents to the new recommendations cited, among many things, the importance of cancer screening in highly touted preventive medicine programs, and limiting government involvement in medical decision making.[46] Breast cancer experts[47] were also quick to point out the shortcomings of the new recommendations. The American Society of Breast Surgeons correctly noted that the new recommendations "effectively turn back the clock to premammography days by making the diagnosis of breast cancer occur only when the tumor is large enough to be felt on a physical exam."[48] The ACOG rejected the new mammography screening recommendations, particularly for the 40 to 49 years age group, noting: "Our experts . . . reviewed all the same data reviewed by USPSTF, but also additional data that the USPSTF did not consider. When recommendations are based on judgments about the balance of risks and benefits, reasonable experts can look at the same data and reach different conclusions."[49] After several months of media scrutiny, about the only people defending the new mammography screening recommendations were the original members of the committee and some economists,[50] although even the latter pointed out that the interface between mathematics and psychology would make it difficult for patients and health providers to accept a "rational" health care economic analysis of the issue. Even the Secretary of HHS was forced to issue a statement acknowledging that the new recommendations were confusing and problematic.[51]

ACOG's disagreement with the USPSTF is no small matter and has enormous implications for clinicians practicing gynecology in the office, because these individuals, along with internists and family practitioners, bear the bulk of the burden of responsibility for screening women for occult breast carcinoma. Fortunately for the medical profession, it appears that the new recommendations have found a suspicious public audience[52] and a medical profession which is going to stay to the course and adhere to established mammography screening standards.[53]

It is important for physicians who practice office gynecology to be acutely aware of the serious limitations of the new breast cancer screening recommendations and understand their significance on multiple levels. For one, the recommendations are simply that—recommendations. As such, they are neither "binding" on practitioners nor do they represent a "standard of care" in either the legal sense or as advocated by medical professional societies which rejected them out of hand. The new recommendations are no substitute for evidence-based medicine or seasoned clinical judgment. There is no separate accounting for family risk factors in the new screening calculus. Furthermore, the new recommendations will do little to improve the liability of ob-gyns for failure to diagnose breast cancer in young women and will likely make an already bad situation worse by increasing pressure on practitioners to pursue otherwise trivial physical exam findings in younger women or mammography findings in older women who have not been screened for now greater lengths of time.

The impetus behind the new breast cancer screening recommendations is a tradeoff between economic and diagnostic opportunity; that is, the willingness to forego a predictable reduction in the number of new cases of invasive cancer in a particular age group in order to decrease the number of biopsies and surgeries for masses or abnormalities which do not turn out to be invasive cancer. Part of the problem with the new USPSTF recommendations is the view the Task Force has of the false-positive result; that is, a finding on mammogram which might be suspicious and which results in surgical evaluation (fine needle aspiration under radiologic guidance or surgical excision) which then turns out not to be a cancer. Although it is not positive in the sense that it is cancer, it is not negative in the sense that "nothing" is found. Although the USPSTF clearly believes that a false positive is a real problem, patients may find biopsy or removal of a suspicious lesion that turns out to be benign reassuring rather than problematic[54] and many if not most patients and medical specialists appear to be willing to put up with the possibility of needle biopsy or surgical intervention and additional imaging if it means that their cancer may be diagnosed at a more curable point.[55]

The solution to this problem should not be to change mammography screening but rather to acknowledge (a) that the only way to definitively rule in or rule out cancer is by obtaining tissue, and this means some sort of surgical intervention; and (b) that some of what propels clinicians to investigate abnormalities is a medical malpractice environment which holds physician liable when they fail to investigate abnormalities on physical examination or mammography.

There has already been significant push back by the academic medical community[56] against the USPSTF's recommendations. Clinicians practicing office gynecology should continue to adhere to older National Institutes of Health (NIH)- and ACOG-recommended guidelines. Doing so will negate any increased medical malpractice liability exposure they would incur by adopting the USPSTF's new guidelines for breast cancer screening, and keep patients and their physicians on the same side in efforts to achieve the earliest possible diagnosis of breast cancer while both parties await new refinements in screening technology.

Appropriate Screening for Cervical Cancer

The establishment of routine cervical cytology screening has had a dramatic effect on the incidence of invasive cervical cancer in the United States over the past

30 years, as evidenced by a decline in the number of new cases of invasive cervical cancer by half. No other malignancy, in either men or women, has had such a dramatic reduction in incidence as a result of a cancer screening program, and the current U.S. approach to screening for cervical cancer is an unqualified public health success. It is important to note, however, that because many of the new cases of invasive cervical cancer in the United States occur in either medically underserved areas or in older patient populations in which individuals may be screened rarely or never, it would appear that the continual manipulation of screening criteria for a population of women who are already being adequately screened is unlikely to significantly further lower the incidence of cervical cancer regardless of the changes made. The number of new cases of invasive cervical cancer in the United States has remained relatively constant for almost a decade regardless of all of the touted advances in superior cervical cytologic analysis and a virtual blizzard of literature on the value of screening for high-risk human papillomavirus (HPV) subtypes.

In December 2009, ACOG revised its recommendations for Pap smear screening for cervical dysplasia. The most dramatic change in the ACOG guidelines from prior years was to initiate cervical cancer screening at 21 years of age, regardless of age at onset of sexual activity. The rationales offered for the change in Pap screening policy were two-fold: (a) screening prior to age 21 years often leads to unnecessary treatment/follow-up treatment and emotional anxiety for young women who are actually at very low risk for developing invasive cervical cancer, so the new recommendations are an effort to achieve better balance in benefit versus harm; and (b) screening prior to 21 years of age often leads to unnecessary and harmful treatment for cervical disease, which has little chance of progression to invasive cancer and a spontaneous regression rate of anywhere from 50 to 90%.[57]

Office practitioners cannot ignore the concept of individual patient risk for the development of cervical dysplasia; the new recommendations do not exist in a clinical vacuum and should not be employed in robotic fashion for patients with traditional risk factors for the development of cervical neoplasia. Rather, office gynecology practitioners should evaluate the new recommendations in light of their patient populations as a whole and judge the applicability for each individual patient.

The new cervical screening recommendations are not binding in any medical or legal sense; they are not definitive evidence of the standard of care in a state court of law for a malpractice action, and they are unlikely to protect a clinician from an unfavorable jury verdict if they have one of the relatively rare patients who develops an invasive cervical cancer during a prolonged "nonscreening" interval.

Clinicians will be held accountable for failures to diagnose cervical cancer, just as they will be held liable for pregnancy-related complications and infertility-related complications from inappropriate use of cervical excisional procedures. For this reason, incorporation of the new guidelines for cervical cytologic screening into routine office gynecology should be done carefully by clinicians on an individualized patient basis to avoid increasing liability exposure, and should clearly be a direct function of the patient population the practitioner is taking care of. The guidelines may not be suitable for clinicians who take care of a young patient population with early onset of sexual activity, multiple sexual partners, high prevalence of sexually transmitted diseases, and poor patient compliance with office visits, regardless of ACOG recommendations as some gynecologic cancer specialists have pointed out.[58] Pap smear screening decisions in young women with multiple risk factors should be individualized. Lastly, office practitioners should remember that even for those with "lower risk" patient populations, the new guidelines do not apply to those women who have a history of HIV, cancer, or who have been diagnosed or treated in the past for cervical intraepithelial neoplasia (CIN) 2 or 3.[57]

In an era where patient expectations for routine office gynecology will likely include a Pap smear and one of the linchpins of patient care will include the practice of preventive medicine, the new recommendations are not currently universally accepted by gynecologists practicing in the office. A more productive approach for clinicians seeking to maximize prevention of disease as well as minimize psychological and surgical harm might be to avoid injudicious use of loop electrosurgical excision procedure (LEEP), and avoid nonindicated HPV DNA testing even if patients request it as well as overreacting to the findings of atypical squamous cells of undetermined significance (ASCUS) on cervical cytology.

The Human Papillomavirus Vaccine

According to ACOG and the American Society for Colposcopy and Cervical Pathology (ASCCP), the new 2009 Pap smear screening recommendations apply to all women in the general population whether they have been vaccinated against HPV or not.[57] Because the longest follow-up data on HPV-vaccinated patients is less than 10 years in duration and some patients will have been vaccinated almost a decade before they will even begin to have Pap smear screening under the new recommendations, any firm conclusion about the validity of the new recommendations in the HPV vaccination era is purely speculative. In all likelihood, the effect of either available HPV vaccine on the future incidence of invasive cervical cancer in the United States is unknown, and will not be known, until there has been at least two or three decades of follow-up[59] and only if there is near-universal adoption of its administration in both young men and women in the appropriate age groups.

Both HPV vaccines (Gardasil and Cervarix) have demonstrated prophylactic benefit against the development

of high-grade cervical dysplasia in large randomized prospective trials, have excellent safety records,[60] and have been demonstrated to have sustained efficacy against HPV for at least 5 years after vaccination in the clinical trials submitted to FDA for U.S. marketing approval.[61] The pivotal role office gynecologists will play as vaccinators for HPV (as well as other vaccines) has been strongly embraced by ACOG[62] even though some experts have expressed reservations about the wisdom of widespread HPV vaccination[63] and the cost-effectiveness of such programs.[64]

There are specific liability issues for office practitioners concerning the HPV vaccine though. Although the side effect profile is very favorable for both vaccines, serious adverse events,[65] and rare patient deaths,[66] have been reported even though the original Biologic License Application (BLA) submitted to FDA in support of approval of Merck's Gardasil did not note all of these. This should come as no surprise because rare adverse events are virtually never detected in clinical trials with fewer than 10,000 enrollees and it is not uncommon for more potential side effects to become known only when a new drug or vaccine is administered to a much larger patient population. Fortunately for clinicians, the HPV vaccine has been designated a childhood vaccine by the Centers for Disease Control and Prevention (CDC) and accepted by the Vaccine Immunization Compensation Program (VICP) as a "covered" vaccine.[67] As such, there is a federally administered program for generously compensating parents whose children are injured by the HPV vaccine provided that the alleged injury is one of those recognized as compensable under the program.[68] Under this program, the vaccine manufacturer is shielded for tort liability claims in state courts and so long as clinicians obtain adequate informed consent for administration of the vaccine, practitioners should be shielded from malpractice actions for adverse events from Gardasil or Cervarix as well. Clinicians must inform parents of minors, as well as those 18 years of age or older who are being vaccinated, of those rare, serious adverse reactions to HPV vaccine administration as part of the informed consent process. Two potential HPV vaccine liability questions remain unanswered at the time of this writing.

The first is whether clinicians who fail to counsel young women about the possibility of being vaccinated against HPV, or who fail to administer the "cancer-preventive" vaccine to young women, will be held liable in tort when one of their patients subsequently develops invasive cervical cancer. The second is whether failure to offer the vaccine or to administer the vaccine to older women ages 27 to 45 years will result in any tort liability should an older patient develop invasive cancer.

Any allegation of malpractice by a plaintiff's attorney in the first setting will be an interesting one, particularly since both HPV vaccines were approved on the basis of reductions in the incidence of squamous as well as glandular carcinoma in situ, surrogate markers approved by FDA as endpoints to measure vaccine efficacy so that the clinical trials to demonstrate the "invasive cancer preventive" benefits of either vaccine would not have to be 10 or 20 years in duration. No patient in any study of any currently approved HPV vaccine—in either the control or the vaccine arms—actually developed an invasive cancer. In any event, this potential liability issue may be readily dealt with by incorporating a counseling session for possible HPV vaccination into the gynecologist's office patient management protocol; if the vaccine is offered and refused after an appropriate counseling session about the potential risks and benefits of vaccination, the practitioner should be protected against potential liability so long as this is adequately documented in the patient's chart.

As for failures to offer to administer, or administer, the vaccine to older women, the issue is perhaps clearer because Merck's application for marketing approval for an indication for administration of HPV vaccine to older women has been denied by the FDA[69] on the basis of a lack of substantive evidence demonstrating the efficacy of the vaccine as a treatment therapy, as opposed to preventive therapy, for older women already exposed to HPV. Should clinicians elect to administer HPV vaccine to older women, particularly those with a history of HPV infection on Pap smear or a history of treatment for cervical dysplasia, several caveats are in order. First, use of the vaccine for such as off-label use is not FDA approved even though it may be incorporated into the routine practice of office gynecology by some practitioners. Second, adverse events resulting from this would not be covered by the VICP. Lastly and most importantly, the therapeutic effectiveness of the Cervarix vaccine in preventing *recurrent* cervical dysplasia in a non-naive patient population was much less than 50%; that is, the vaccine works relatively poorly (at least compared to its prophylactic effect in virus-naive women) in the treatment setting. (See the BLA application data on the FDA website, available at www.cber.fda.gov. This data has been presented to ACOG by representatives of Merck.) Clinicians must be sure to inform older patients of the lower probability that use of the vaccine will prevent the development of recurrent high-grade dysplasia or invasive cervical cancer and be sure that this counseling is documented in the patient's chart.

One final issue relating to HPV vaccine administration relates to the role of vaccination in prevention of HPV-related noncervical cancers. FDA has approved Merck's Gardasil for two additional indications: the prevention of HPV-related vulvar cancer and prevention of HPV-related vaginal cancer. These approvals were based on data showing a decrease in the incidence of vulvar dysplasia in women who had been vaccinated when compared to local controls. Because of the relative rarity of vaginal dysplasia and cancer compared to vulvar neoplasia, the data on vaginal cancer is much less robust.[70] Although these two additional indications represent another potential benefit of HPV vaccine administration, office gynecologists should be aware of the fact that the

use of surrogate markers (prevention of severe dysplasia presumably reflecting prevention of invasive cancer) in two diseases that are rarer, and typically occur in older women compared to the disease of cervical cancer, is fraught with even more uncertainty when counseling patients about the benefits of vaccine administration.

SCREENING FOR GENETIC DISEASE

The ability to screen for genetic disorders has advanced rapidly over the past two decades. The difficulty for the obstetrician-gynecologist lies in keeping up with the rapidly advancing technology and current recommendations for testing at various life stages, for example, preimplantation, antenatally, postnatally, or among adults. Conventional cytogenetic analysis in the form of G-banded karyotype has a resolution of 3 to 10 MB, whereas fluorescence in situ hybridization (FISH) can be used to detect chromosomal abnormalities less than 3 MB.[71] Array comparative genomic hybridization (CGH), which is not limited by the need for dividing cells as in karyotyping nor by the number of abnormalities that can be screened for at one time, can detect small chromosomal abnormalities. Although the average obstetrician-gynecologist cannot be expected to have an advanced knowledge of these techniques, some rudimentary understanding of the available options is necessary in order to guide patients properly and refer them as appropriate.

Preconception and Prenatal Genetic Diagnosis

The ability to test individuals for the presence of genetic disease carrier states prior to conception allows for more informed family planning decisions. It is up to the physician providing preconception or prenatal care to screen patients for potential genetic disorders based on risk factors. Ethnic background is the most common "red flag" a provider will encounter when determining what genetic testing to offer a patient. African American women should be offered carrier testing for sickle cell anemia, whereas women of Mediterranean descent should be offered testing for thalassemia. For those individuals of Eastern Europe Jewish (Ashkenazi) descent, there are a number of recessive genetic disorders for which preconception carrier testing is recommended, including Tay-Sachs, Canavan, and Gaucher disease. According to ACOG guidelines, cystic fibrosis carrier screening should be specifically offered to all Caucasian couples (including Ashkenazi Jews) planning pregnancy or presenting for prenatal care due to the high percentage of carriers in this population and should be made available to all other patients.[72]

Family history of genetic conditions also raises a concern and generally should result in a recommendation to undergo genetic counseling and possibly sophisticated genetic testing. Genetic counseling and testing for disorders such as fragile X syndrome, the most common inherited form of mental retardation, need only be offered to patients with a family history of mental retardation or fragile X mental retardation.[73] If a patient carries a known fragile X permutation, prenatal testing should be offered to determine if the fetus is affected with the disorder.

Testing for the Gynecologic Patient

Many women present to their gynecologist with a family or personal history of breast cancer and inquiring whether or not they need to undergo testing for the *BRCA1* or *BRCA2* gene. Alternatively, some patients may have undergone testing using an "at-home" test kit and present to their physician requesting interpretation of the results or surgical intervention based on their belief that they are at high risk for breast or ovarian cancer. Most general obstetrician-gynecologists do not have the qualifications to appropriately counsel patients regarding their genetic testing results, and FDA has expressed serious concerns about the accuracy as well as marketing of unapproved genetic tests.[74]

The most critical point for the general obstetrician-gynecologist is recognizing when a patient should be referred to a center with expertise in genetic counseling and/or testing center. The complexity of today's genetic tests make it unlikely that the average practitioner will have the resources necessary to provide advanced genetic counseling services in their office. In this circumstance, referral of the patient to a specialized center not only ensures the patient will receive the information necessary to make an appropriate decision about whether to pursue genetic testing but also prevents assumption of liability on the part of the general obstetrician-gynecologist for failure to recognize the importance of screening or the significance of testing outcomes. Of course, this does not mean that the office-based practitioner is absolved from all responsibility with regard to the performance of the test. It is necessary for the provider to understand the results of the test and its potential impact on the patient's health and well-being, including the patient's psychological health, such that the physician is able to provide appropriate care and support for the patient.

Whether office practitioners are also legally responsible for results patients obtain from kits they purchase themselves or from outside testing opportunities (e.g., "spit parties") is an unanswered legal question; given the paucity of information about the accuracy of either the tests themselves or the medical claims they make, office physicians should indicate the possible limitations of such testing and either avoid discussion (explaining why) or refer patients to a genetic counselor for a full discussion.[75]

Ultimately, the result of not providing a referral for genetic counseling and/or genetic testing could be litigation, either as a simple medical malpractice tort action or in the

form of a "wrongful life" lawsuit. Although not permissible in all states, the essential theory of wrongful life suits is the assertion by the parents that a child born with a detectible genetic disorder would have been aborted had the parents known about the child's condition in utero. In order to appropriately diagnose children that might be affected by a genetic condition prior to delivery, while simultaneously avoiding liability, means that a practitioner must follow ACOG guidelines as to what prenatal genetic diagnostic testing should be offered based on each couple's unique history and risk factors.

For any physician ordering or referring a patient for genetic testing, a basic knowledge of the protections afforded the patient under federal law is essential. ACOG *Practice Bulletin Number 103*, *Hereditary Breast and Ovarian Cancer Syndrome* admonishes the physician that "an important aspect of genetic counseling is discussion of current legislation regarding genetic discrimination and the privacy of genetic information."[76]

Currently, there are two primary sources of federal law impacting privacy, nondiscrimination and individual genetic information. The HIPAA discussed earlier in the chapter provides some basic protections to prohibited use of genetic information; however, HIPAA applies only to employer-based and commercially issued group health insurance. The Genetic Information Nondiscrimination Act of 2008 (GINA) modified the HIPAA privacy requirements and extended the protections provided to patients with a personal or family history of genetic disorders.[77]

GINA prohibits discrimination by employers or health care insurers based on an individual's genetic information.[78] For purposes of the statute, genetic information is defined as (a) an individual's genetic tests, which would include any testing completed as part of a research study; (b) the genetic tests of an individual's family members, including dependents and up to, but not including, fourth-degree relatives; (c) genetic tests of the fetus of a pregnant family member or an embryo of a family member participating in assisted reproductive technologies; (d) family history of any genetic disorder; and (e) a request for, or receipt of, genetic services or participation in clinical research that includes genetic services by an individual or family member.[78] Genetic information does not include a patient's age or sex.

Although GINA prohibits discrimination on the basis of genetic information by health care insurers, it does not mandate coverage of genetic testing nor does it provide protections from discrimination in determining life, disability, or long-term care insurance. In addition, although health care insurers cannot refuse coverage, they are permitted to determine premium rates with consideration of genetic conditions.

The ability to detect genetic predisposition to disease or the presence of genetic conditions will only increase in the coming years as the technology continues to advance. The practice of general obstetrics and gynecology is deeply impacted by these developments, and it is imperative that practitioners understand both their obligations with regard to counseling and screening as well as when they should refer patients to other specialized providers, such as genetic counselors, to ensure patients receive the most accurate information to aid in the decision-making process.

SOME MEDICAL-LEGAL ISSUES SURROUNDING ELECTRONIC MEDICAL RECORDS

Liability for Use or Nonuse of This Technology

The development of electronic health record (HER) technology for both patient use (personal health records [PHRs]) and health care institution storage of data (EHRs) has become a major trend in the health care arena in the past several years. EHR may be defined as "a [digital] collection of health information that has been gathered by and is managed by an enterprise such as a doctor's office or hospital." The push for the implementation of EHR has been championed as both a cost-cutting measure and as one of several tools which will improve efficiency in health care delivery as well as improve patient safety.[79] It is the latter's purported benefit which raises the specter of creating additional liability for physicians if use of EHR is viewed as a necessary component for "best practices," "pay for performance," or federally mandated standards of medical care.[80]

The use of EHR opens up entirely new areas of potential liability for office practitioners. This increased liability for physicians could theoretically arise under three distinctly different circumstances: (a) the failure to use EHR in the physician's office (with attendant limitations on timely transfer of and access to comprehensive patient health information) or liability for failure to use the most modern medical technologies; (b) the use of EHR by the physician's office but the failure to read or review all of the information contained in the patient's EHR; and (c) unintentional or erroneous release of confidential patient information contained in the EHR.

How the localized set of individual state medical malpractice rules and cases will be applied in the new domain of EHRs is difficult to predict given the fact that (a) there is no agreed upon best practice or professional consensus; (b) there is enormous variation in use of the technology from jurisdiction to jurisdiction; (c) there is no "interoperability" of a system across jurisdictions; and (d) there has been no consensus as to how to protect confidential patient information contained in EHR from unwanted disclosure. Allegations of medical malpractice relating to EHR thus far are rare events, in large part for the following reasons: problems with interoperability of EHR among different hospital systems (or even among different hospitals within the same system), the lack of consensus about which EHR is best for a particular

physician practice setting, the still low adoption rate of EHR systems into physician practices despite federal incentives, and the failure of many EHR to incorporate all of the diverse medical information patients may have from different health providers working out of different nonconnected hospital and office locations.

If EHR were considered "routine care," or more aptly the standard of care for medical practice, then a duty to use EHR information nonnegligently should follow. This duty could be breached by either (a) refusing to base one's practice on EHR or (b) failing to adequately review a patient's EHR. This is not a minor concern. Although the current standard of care for physicians is to review relevant available patient records—whether paper or electronic—at the time of consultation, the sheer volume of material which could conceivably be contained in an EHR might exceed the physician's ability to adequately review it in the time frame of an office visit. The extent to which the law would adapt the duty of the physician to review records to the torrent of information potentially available in an EHR is unknown. In addition, the EHR might contain information which the physician might not normally encounter, such as screening for rare genetic diseases a primary care physician might not be familiar with, yet it is theoretically possible that the physician might nevertheless be held accountable for being knowledgeable about them.

In *Das v Thani*, a case adjudicated in New Jersey Supreme Court,[81] two lower court rulings in favor of the physician were overturned by the state's highest court in an obstetrical malpractice case involving the use of "maternal" monitoring of labor instead of the decades old practice of electronic fetal monitoring. This case may have implications for the issue of potential medical malpractice liability for physicians who fail to employ the "latest" medical technologies, whether the medical practice involves more established medical technology such as fetal monitoring or the latest potential medical technology such as EHR.

In its ruling on the issue of how a jury is to be instructed in distinguishing between "the genuine exercise of medical judgment and a deviation from accepted practice,"[82] the New Jersey Supreme Court held that in order for the physician to prevail in arguing that his medical practice was merely the legitimate exercise of his professional judgment, the jury needed to be first instructed that there was sufficient evidence that the practice (in this case, maternal monitoring of fetal movement) was an equally acceptable medical practice to the more prevalent and more modern alternatives (in this case, electronic monitoring of the fetal heart rate).[83]

One possible reading of the case is that a physician can be found liable for medical malpractice by a jury simply for not using the most "modern" technology, even if the medical literature does not support claims that the technology improves patient outcomes or if there is no uniform consensus in the medical profession as to how it should be used.[84] As is the case with electronic fetal monitoring, even after decades of use, there is still no definitive evidence that use of the technology has significantly decreased the incidence of birth-related anoxic brain injury to the newborn even though some professional societies such as the ACOG both advocate its use in some obstetrical situations as well as acknowledge its limitations in interpretation.[85] One might read the case more narrowly, however, as holding that if the pre-existing standard of care *require*s use of a particular technology, the jury must be instructed that it is not a matter of "judgment" for the physician to use alternative technologies.

One caveat regarding the cited case is the fact that the case is binding law only in the State of New Jersey. Although it is not uncommon for lawyers to use cases from other jurisdictions to bolster their arguments, especially in cases of first impression in their own states, this is not always the case: New Jersey has a reputation as a bit of an outlier on medical malpractice issues.[86] Although cited numerous times within New Jersey, in the 7 years since its issue, the *Das* case has only been cited once outside it, in neighboring Delaware.

The fact is that use of EHRs has not been embraced as "the standard of care" by any professional society even if the consensus at the federal and hospital levels is that there will be an inexorable move in that direction for most if not all parties concerned. Nor have professional societies or the federal government favored one EHR product over another, agreed on a standard, or solved problems about interoperability or patient medical information privacy concerns.

Once these problems are resolved, and use of EHR is the standard of care for "ordinary" practice, it is likely that eventually physician medical malpractice liability will follow. If the U.S. government eventually requires the use of EHR, then liability issues for physicians will certainly arise. This will be true for physicians who have access to EHRs and fail to use them, or for physicians who simply refuse to use EHRs even if they are the standard of care. Until that time, however, office gynecologists should be aware of the potential for the increasing availability of EHR to increase their potential liability exposure on multiple levels. One pre-emptive strategy may be for patients to be informed when they sign in for an office visit that the physician will only be reviewing portions of the EHR, which he or she deem, in their medical judgment, to be relevant to the office visit and are not accountable for explaining all information in the EHR, particularly if it is far afield of their training. For office gynecologists who are also the patient's primary care physician, this will be a more difficult argument to make.

Issues Concerning Physician and Patient Use of the Internet

The Internet has changed the practice of medicine and impacted on the control and availability of medical information which used to define the traditional, one-way

physician–patient information in so many ways that a comprehensive review of this topic could be the subject of its own book. The ready availability of virtually unrestricted and essentially unregulated official and unofficial medical information has for the first time placed patients in the position of potentially knowing almost as much factual information about their diseases or medical care as their physicians.[87] This may actually be a good thing, providing one more incentive for physicians to stay current on what is in the medical literature. On the downside, physicians in the office may find themselves having to dissuade patients from believing everything they read in the medical literature on the Internet or explaining that what patients think they read is neither the standard of care nor completely accurate. Then again, this may be viewed as all part of patient education by the physician. There are several less publicized aspects of the patient-physician-Internet connection to be considered however.

The use of any electronic highway is always a two-way street. Patients may surf the Internet for information about their diseases, planned gynecologic or obstetrical surgery, or for general health information or information about prescription or over-the-counter medications. Patients may also surf the Internet for information about the gynecologist they are seeing in the office. Physicians should be mindful of their web presence; the latter includes not just the professional medical website(s) they may appear in (e.g., the webpage for the obstetrics-gynecology department of the hospital or medical school they are affiliated with) but also the personal information and results which patients may obtain if they "Google" the physician's name or go to Facebook.

As a rule, physicians should get in the habit of conducting a web search of themselves so they can see what information they are linked to and what current and prospective patients will see if they seek out information about them.[88] Just as important, physicians should be aware of nonmedical information about them that is on the Internet and which patients and nonpatients may discover. Readily available personal information about a physician goes far beyond facts around his or her education or practice(s), such as his or her board certification or disciplinary actions by state medical boards or federal agencies. With relatively little effort, it is possible to find a physician's home address and information about the purchase price of his or her house, market value, and domestic issues such as divorce actions or history of substance abuse.[88]

The ideal strategy would be to avoid having a "personal" web presence altogether, but this is not a realistic consideration for most physicians. The bottom line is that physicians should be prepared to discuss medical malpractice settlement information and issues about them, which are in the public domain as well as be prepared to deal with boundary issues when patients bring up inappropriate personal information that is only remotely or totally unrelated to an ongoing physician–patient relationship.

The availability of medical information on the Internet, particularly the promotion of certain types of dietary supplements and alternative medical therapies which are not directly regulated by the FDA may create liability issues for physicians as may the off-label use of FDA-approved medications or surgical procedures. Physicians may incur malpractice liability under the "learned intermediary doctrine" for adverse events related to dietary supplements they strongly promote or for prescribing medications for off-label usages. Physicians should be aware of what is advertised or contained in Internet information for off-label uses of medical products or alternative medical therapies.

A perfect example of this is the issue of prescriptions for pharmacy-compounded bio-identical hormone therapy for menopausal women.[89] Numerous large compounding pharmacies have been cited by FDA, and many more not disciplined, for making safety and efficacy claims about their products on websites which are either misleading, known to be false, or completely unsubstantiated. Worse still are claims of superior efficacy and safety compared to prescription drug products manufactured by pharmaceutical companies despite the lack of any substantive evidentiary basis in the medical literature and which have never been prospectively tested in large clinical trials.[89] Despite this, patients may insist on prescriptions for these products in part based on this incorrect information or because they hate commercial drug manufacturers or because they want "more natural" products. Office gynecologists are obligated to know the medical literature on this important topic and should be familiar in at least general terms with the information patients are seeing on the Internet about products they are prescribing. If providers elect to prescribe compounded hormone therapies, they should document the limitations of these medications and the precise counseling they provided to the patients.

The Internet has changed the practice of medicine for the better through the availability of two-way teleconferencing, allowing two health care system problems to be addressed: (a) the general lack of physicians, particularly subspecialists, in some rural areas in the United States; and (b) the unacceptably long wait patients must occasionally endure to see a primary care physician in both urban and rural areas. Video teleconferencing between rural and urban academic physicians is now accepted medical practice in parts of the United States, and such activity is governed by specific rules and regulations promulgated by individual state medical boards. Rural physicians are now routinely able to consult with specialists in regional medical centers to improve direct patient care as well as help alleviate some of the patient care problems (e.g., long waiting times) associated with the relative lack of physicians in some parts of the United States.[90]

The pressing need for timely medical care in urban areas and the relative lack of medical services or specialized services available only at great distance away for patients in rural areas have both pushed Internet teleconferencing to a new level within the past year and resulted in the development of teleconferencing services between physicians and individual patients.[90] For example, in Texas OptumHealth, a division of insurer United Health Group, offers a service called NowClinic which allows patients to consult with physicians via two-way teleconferencing over the Internet. Patients who want to use this service must first register online, provide basic medical and credit card information, and accept a $45.00 charge for a 10-minute virtual visit.[91] Patients may receive prescriptions for some medications but not for controlled substances. Most of such interactions are not covered by patient insurance plans; the growing popularity of Internet-based medicine may be based, in part, on the fact that it is a cash business.

What has not been worked out completely in telemedicine care are some of the potential physician liability issues. It is unclear whether a physician prescribing a prescription for a patient after an online visit constitutes an acceptable standard of care as well as whether a legitimate physician–patient relationship can be established via the Internet if the patient and physician have not previously met in person. Individual state medical boards are still working out operating rules for dealing with these new developments. The trend strongly suggests that physicians will likely be held liable for any untoward events that result from purely electronic encounters. It is also possible that Internet prescribing of medications absent actual physical contact with the patient may be found to be below the acceptable standards of care; whether a physical examination can be conducted in cyberspace is an ethical and medical-legal question which will likely be resolved at the state court level once Internet-based treatment complications occur and physicians are sued.

Physicians who currently engage in Internet-based diagnosis and prescription writing should recognize that in the absence of hands-on examination, they may be open to malpractice liability that may ultimately prove to be difficult to defend in court if their respective state medical boards have determined that such medical practice falls below the accepted standard of care and if untoward events occur as a direct result of practicing Internet-based medicine.

ISSUES RELATING TO MEDICAL MALPRACTICE LITIGATION AND DEALING WITH LAWSUITS

The standard of medical care for physicians is a function of multiple factors such as national practice patterns and recommended clinical guidelines from medical specialty societies such as ACOG. Such guidelines are generally, but not always, grounded in evidence-based medical experience, and although informative on what the prevailing medical standard might be at a given moment, they are not considered dispositive on whether an individual physician's conduct falls below the standard of care by either judge or jury. This is because the ultimate arbiter of what the current standard of care actually is in a particular jurisdiction is actually what local juries and judges decide in individual malpractice cases.

Because there are no published federal medical practice guidelines and little or no federal medical malpractice law, the determinations of what is required of physicians to avoid liability for medical malpractice are all "local." Although there is a trend at the legislative level toward having published "national" government standards, nothing has gotten out of Congressional committee. Despite current federal discussions about cost savings, patient safety, and minimizing regional differences, it may be that the push for federally mandated published "uniform" medical care standards represents a level of micromanagement of the medical profession and intrusion by the federal government into the physician–patient relationship that no administration is willing to push.

A number of fundamental points about the practice of medicine, clinical guidelines for care in medical practice, and terminology need to be discussed. One of the first points which must be made is that although there are instances in which the federal government or federal courts (particularly the Supreme Court) have weighed in and "micromanaged" the medical profession by proscribing certain practices or procedures, in general, the regulation of the medical profession is done at the state level by individual state legislatures and individual state medical boards. Similarly, the overwhelming majority of medical malpractice case law and precedent is generated at the individual state court level, usually at the lowest level court in a particular jurisdiction, with wide variations in what is determined to be conduct below the standard of care. Although there may be national standards (usually by consensus) for medical practice or suggested guidelines published by medical societies, the actual state court determination in a particular jurisdiction may have little bearing to what is actually going on nationally. As with politics, most medical malpractice, as well as most medical practice, is local.

Individual state legislatures can and routinely do pass bills which by statute regulate some aspects of medical practice. For example, in many states, the legislature has passed requirements for informed consent for specific surgical procedures such as hysterectomy and tubal ligation. In such instances, a state legislature can set up very specific requirements affecting widespread medical practices. The state legislature and the individual state medical board are responsible for defining basic medical jurisprudence and the basic principles of medical

practice for that state, with individual state court medical malpractice decisions filling in the gray areas.

Not surprisingly, there is a great deal of individual variation from state to state in medical practice decisions even if physicians embrace the general concept of uniform standards of care for particular medical specialties on a national level. Although there may be national standards of care for management of select medical conditions published by professional medical societies, it is rare for them to specifically state that a recommendation they have made as part of a clinical guideline is the *only* proper way for a physician to care for a particular patient. This general policy not only leaves room for physicians to practice medicine on a more individualized basis but also places patients in the position of possibly being exposed to medical practices that may be outdated, discredited, ineffective, or unnecessarily dangerous compared to other therapies that are more accepted. The general notion that there are specific local standards of care, as opposed to national standards, rests in serious tension with the nature of medical school training, postgraduate education, and the structure of specialties and subspecialties throughout the United States.

Our courts profoundly affect the standard of care through rulings in particular medical malpractice actions. The landmark case of *Canterbury v Spence*[92] established the notion that the amount of information required for adequate informed consent which must be provided by a physician to a reasonable patient is one which is determined by the courts, not the medical profession itself. Although only about half of the states in the United States use the "reasonable person" standard of *Canterbury v Spence* (the remaining states use a "reasonable physician" standard),[93] both standards are objective standards which allow juries and courts to make decisions based on either what a reasonable patient would want to know or what a reasonable practitioner would want to disclose.[94]

Practice guidelines remain important sources for possible standards of care.[95] Although they are neither statutes nor regulations and are not considered definitive evidence of what individual clinical practice should be, practice guidelines published by professional societies are evidence of the practice goals the medical profession has established for itself in efforts to foster good patterns of professional conduct and improve patient safety. As such, they are a potentially important element in court in establishing a "legal" standard of care and could be mentioned at trial.

Physicians practicing office gynecology should be familiar with published clinical practice guidelines by ACOG and other relevant professional societies. Clinical guidelines for "best practices"—whether proposed by medical professional societies, federal agencies such as the Center for Medicare and Medicaid Services, or pharmaceutical or medical device manufacturers—must all be viewed through the prism of individual patient comorbidities and illnesses. Careful consideration of such clinical recommendations must also be tempered by the fact that there is the possibility that physicians from both academic medicine and the private sector serving on expert panels may have strong ties to the pharmaceutical, medical device, or biotechnology industries and may have undisclosed conflicts of interest.[96] At the present time, the Institute of Medicine of the National Academy of Sciences is reviewing the problem of expert panel conflict of interest and considering new recommendations as to how better regulate such conflicts of interest.[97]

The Medical Malpractice Suit: Process and General Remarks

Being sued for medical malpractice is one of —if not the most—unpleasant and stressful experiences even seasoned clinicians are likely to face in medical practice.[98] Suing obstetrician-gynecologists for medical malpractice is so common an occurrence (89% of ACOG fellows have been sued at least once in their careers)[98] that for all intents and purposes, practicing ob-gyn physicians should view the possibility of medical malpractice litigation and the necessity to have malpractice insurance coverage as the price of doing business. Still, medical liability continues to be viewed as an ongoing nemesis by obstetrician-gynecologists.[99] Although it might be tempting for clinicians practicing just gynecology in the office setting to eschew medical malpractice insurance coverage, ACOG has recommended that individuals with gynecology-only practices maintain insurance coverage including obstetrics, even if they do not work in the operating room,[100] because first trimester pregnancy care is often within the scope of such office practices.

Several excellent guidance documents are available to physicians facing medical malpractice litigation and how to cope with the often several year-long process involved in settling a lawsuit.[101] Although a comprehensive review of all aspects of the entire litigation proves is beyond the scope of this chapter, there are several important points, and some new trends, which should be discussed.

First, all of the medical records kept in the office on a patient suing a physician are critical and discoverable. This includes the chart (whether paper or electronic), all hospital records, all prescription records, and any written and electronic correspondence. Office practitioners should resist the temptation to send angry or "corrective" e-mails to patients or their attorneys. Most importantly, under no set of circumstances should any written or electronic record be altered in response to being served with a complaint from a patient's attorney. There is nothing wrong with dictating a carefully worded and objective addendum to the medical record; office practitioners must not forget that every single part of the patient's record may be subject to line by line

interpretation by plaintiff's counsel at trial, taken out of the context of the entire chart, and blown-up on a large poster for the judge and all members of the jury to see. In group practices, it is important for fellow practitioners to be aware of potential malpractice litigation of associates and for all parties to understand that the medical group collectively will bear the brunt of injudicious or angry responses to litigious patients or their counsel.

Disclosure of Adverse Outcome and Physician Apology Laws

Even if an ob-gyn confines his or her gynecologic practice to the office and never sets foot in the operating or delivery room, adverse events from procedures, prescriptions, or patient general care will inevitably occur. Patient safety "experts" and health law policy gurus inevitably tout (a) the merits of a policy of full disclosure of adverse events both for strengthening the physician–patient relationship and promoting patient safety and higher quality health care and (b) a policy encouraging "physician apology" for any adverse event. Given the mixed reception efforts at medical malpractice reform have encountered nationally and the enormous variation in where individual states are heading on tort reform (ranging from favorable long-standing caps on damages in California and more recently Texas to distinctly unfavorable rejection of efforts to limit compensation for pain and suffering in states such as Illinois,[102] it is easy to see why any potential additional remedy to the problem of medical liability might be advocated.

ACOG has taken the reasonable position[103] that there is a difference between an expression of sympathy for an untoward event and an apology for an adverse event which is clearly not the result of medical negligence. Although the first is always appropriate, the latter suggests that the physician is accountable or responsible in a liability sense for any unsatisfactory outcome, and this may not be the case because adverse outcomes or complications can and will sometimes occur even when the medical care delivered meets or exceeds the standard of care or even the "best" level of care one might contemplate.

Under such circumstances, an apology is neither indicated nor appropriate, although an expression of remorse about the adverse event itself and openness about the occurrence of such an event are appropriate and should be encouraged. This is because a lack of clear and honest answers about what happened is one of the reasons why families sue physicians[104] and because other physicians may be the source of comments about substandard care.[104]

ACOG has supported programs which encourage patients to directly discuss both injuries and errors with patients,[105] but other opinions assert that apologies should be considered, and offered, only on an individual case-by-case basis and not as routine conduct for every adverse event. At the present time, apologies are not permitted to be construed as or offered as evidence of an admission by the physician that he or she was negligent in a court of law, but health professionals must remember there is no guarantee that individual state laws governing this will not change.

These considerations aside, it is always important to be honest about adverse events and to both acknowledge to the patient that it occurred and to provide a straightforward, honest explanation about the events which transpired. Physicians should also be aware that "physician apology laws" vary from state to state,[106] as do the particular philosophies of individual insurance carriers (and physician employers). Physicians must be familiar with their obligations under the laws of the state they are practicing in as well as any organizations they work for. Whether physicians are practicing in a jurisdiction which has physician apology laws or not, one thing which is clear is that a policy of apology cannot work alone and must be coupled with an organized program of information transparency and risk management by the institutions and practices the physician is affiliated with.[107]

The Expert Witness: Our System and a Necessary Evil That Cuts Both Ways

That the medical malpractice litigation system is unfair, inefficient, expensive, frequently does not compensate individuals who have been injured by real malpractice, has not markedly improved patient safety and has affected medical practice patterns for obstetrician-gynecologists practicing in areas characterized by high premiums[108] are well-known facts.[109] As gatekeepers, judges have the ability to allow medically misleading, inaccurate, or incorrect expert witness testimony into court. Juries generally lack the sophistication or training to understand "dueling experts" when complicated medical issues such as birth-related cerebral palsy are being contested in court. At the end of the day, juries may know little more than that the patient suffered a grievous injury, even if the link to malpractice is tenuous. Juries also know that physicians carry malpractice insurance and are not directly responsible for paying for damages, so they may feel like the physician is not going to be directly "hurt" by awarding damages to an injured patient even if they are doubtful about whether the patient's care fell below the standard of care.

Integral to all of this is the expert witness for the plaintiff and the defense. Without expert witness testimony, juries are not allowed to decide if the defendant physician's conduct was negligent; that is, fell below the "standard of care" and clearly resulted in the damage which occurred, or allegedly occurred. This holds true except in "res ipsa" cases; that is, those which speak for themselves such as cutting off the wrong limb or leaving a surgical clamp or sponge in the abdomen that

do not require experts for juries to determine that the standard of care was breached by the physician's conduct. Although the obstetrical literature has repetitively focused on the concept of "hired guns" for plaintiffs' attorneys suing physicians and on occasion accused them of providing biased testimony in exchange for favorable testimony,[110] in all likelihood there is also questionable expert witness testimony offered in defense of physician conduct and just as much financial incentive for defense experts as well.

There has been no clear way forward for decades to resolve the malpractice litigation mess. Alternatives to litigation such as "medical malpractice courts," mandated alternative dispute resolution, administrative compensation for adverse medical outcomes,[111] and early settlement offer after adverse event disclosure[112] have been discussed for years with little real progress at implementing these external fixes to a broken system. In some states, independent review of malpractice cases is either strongly urged or required prior to allowing a case to proceed to civil trial; although the findings of such review panels are not dispositive, their findings can be admitted as evidence at trial. Alternatives to trial in civil court have been suggested for decades, although it is highly unlikely that a serious alternative to our adversarial medical malpractice trial system or malpractice tort reform at the federal level will emerge in the foreseeable future. Reasons for this may include medical malpractice is a big legal business in most states, U.S. tort law tradition revolves around the concept of attempting to make injured clients "whole" by awarding financial damages, and there is no core of civil servants with sufficient training in both law and medicine to skillfully decide such cases.

One internal reform aimed at correcting some of the expert witness testimony abuse issues which have plagued obstetric-gynecologic practice for decades has instead focused on raising the bar for both the substantive content of expert witness testimony as well as the qualifications for what makes an appropriate expert for malpractice testimony. ACOG has proposed guidelines for the testimony content and medical qualifications of experts.[113] (ACOG criteria for expert witness testimony can be accessed at www.acog.org/~/media/Departments/Members%20Only/Professional%20Liability/ExpertWitnessQualifications.pdf?dmc=1&ts=20130418T1756058504).[113] These guidelines are more stringent than the more relaxed standards state civil courts use to screen potential expert witnesses under the *Daubert* rules.[114] (The *Daubert* standard is a set of guidelines used during U.S. federal legal proceedings to determine if an expert witnesses' testimony is admissible. See Table 30.1 for a list of these guidelines. Although the *Daubert* standard is now the law in federal court and over half of the states, the *Frye* standard remains the law in several jurisdictions, e.g., California, Florida, and New York. The *Frye* standard provides that expert opinion based on a scientific technique is admissible only where the technique is generally accepted as reliable in the relevant scientific community.)

TABLE 30.1 Guidelines for the Admission of Expert Witness Testimony Based on the *Daubert* Standard

The judge is the gatekeeper and makes the preliminary assessment of whether the scientific expert testimony is based on scientifically valid reasoning or methodology and is applicable to the facts being considered.

The validity of the methodology or reasoning is determined by considering if

a. The theory or method can be and has been scientifically tested
b. Has been subject to peer review and publication
c. Has a known or potential error rate
d. Standards exist that control the operation of the technique or methodology and these standards are maintained
e. It has gained widespread acceptance in the relevant scientific community

From *Daubert v Merrell Dow Pharmaceuticals, Inc.*, 509 US 579, 589 (1993).

Liability Issues for Nontraditional and Innovative Office Surgery

Increasingly, gynecologists are turning to other office-based services to supplement income in a time of decreasing medical reimbursements. Cosmetic or aesthetic surgical and dermatologic procedures are popular options and include such things as laser hair removal, microdermabrasion, and fillers. There is concern over whether the physicians providing these services have the experience and training to safely perform them. There is also a possibility of potential personal liability for damages if the provider's malpractice policy does not provide coverage for these procedures or if such coverage is denied. Engaging in a rigorous informed consent process may help insulate a practitioner from this liability; however, it is unclear whether disclosure of a physician's limited credentials to perform cosmetic procedures would prevent a generous jury verdict on behalf of the plaintiff.

Even more concerning is the provision of these services to the public by providers without any medical training, also referred to as nonphysician clinicians (NPCs).[115] In these arrangements, a physician is usually employed by a spa as a "medical director," thereby enabling the spa to order medical devices and drugs for the procedures performed in the spa. Unfortunately, a physician acting as medical director in this capacity is almost always off-site and provides no supervision to the NPCs. These types of arrangements put patients in jeopardy and subject the physician to significant liability.

CONCLUSION

ACOG has recognized for years that the problem of patient safety, and the surrounding potential medicolegal issues that may arise, in the office gynecology practice setting is a serious one.[116] As with other subspecialty medical societies, the College's renewed emphasis on

patient safety attained greater momentum with the publication of the Institute of Medicine's[117] 2000 report *To Err Is Human* and all of the accompanying adverse publicity in the press about medical errors and safety concerns in both hospital- and office-based medical practice. These concerns remain particularly relevant for physicians practicing office gynecology.

The primary safety concerns for office-based gynecology procedures include adequate informed consent, full disclosure to patients about the nature of the contemplated procedure as well as available alternatives, whether the procedure is the standard of care or "investigational," and a comprehensive discussion about potential side effects and benefits as well as potential conflicts of interest on the part of the treating physician. Efforts must be made to ensure that patient comfort and safety are maximized by providing appropriate levels of anesthesia for the procedure as well as suitable safety equipment to manage unexpected cardiovascular events.[118] Patient safety and medical equipment checklists should be a routine part of office gynecology surgical practice in order to maximize patient safety, particularly from equipment malfunctions. Office space and facilities should be available to allow patients to recover from procedures under adequate supervision. Careful attention must be paid to follow-up instructions, responsibilities of family members if they are assisting in care, and clear lines of communication between the patient and the office should problems relating to office-based medical or surgical care arise.

CLINICAL NOTES

- Most physicians, patients, and health policy experts also believe that HIPAA's "privacy rule" protects medical confidentiality and likely assume that the confidential information contained in the medical record is *protected* from access by HIPAA, but in reality, HIPAA is also a *disclosure* act that provides unanticipated and unwelcome access to patient information by a plethora of health care–related institutions and individuals.
- The HIPAA rules also permit physicians, nurses, and other health care professionals to disclose protected patient information for treatment purposes without patient authorization.
- All relevant physician office forms should clearly and legibly indicate that the physician, his or her office personnel, and practice *cannot* be held responsible for what insurance carriers do with the private patient information they, by law, have access to.
- Simple ways to avoid liability in the office gynecology setting include accurate and timely record keeping, preservation of patient confidentiality (particularly if conversations can be overheard), compliance with HIPAA disclosure requirements, having a staff who treats patients with respect and courtesy in all interactions, and professional conduct by all health practitioners in the office at all times.
- Maintenance of board certification may be a requirement for obtaining a state medical license, obtaining hospital privileges, or being added to a list of providers for insurance companies or a health maintenance organization.
- Physicians and other providers must be aware of what the medical jurisprudence requirements are in the state or states they practice in. For example, some states have specific consent forms that must be used for all hysterectomies or tubal ligations, and reporting requirements for communicable diseases or cases of intimate partner violence vary across states.
- Patients have now rightfully come to expect that treating physicians and physician-investigators be transparent about their vested financial interests in any medical or surgical therapies/devices they are recommending, whether their care is occurring in a traditional practice or clinical research setting.
- Providers should be aware that what constitutes innovative medical practice is not precisely defined in either the medical or legal literature and occupies a legal and regulatory "gray area" between standard therapy and organized clinical research, thus representing an ill-defined area of potentially increased medical liability exposure.
- Planned deviations from standard office medical or surgical practice require informed consent specific to those planned interventions so that patients can be appraised of their treatment options as well as the unique potential risks (and benefits) innovative therapy holds.
- Both the American Medical Association and ACOG support the concept of physician conscience claims as a reason to refuse provision of certain medical services, and both organizations have stated that physician refusal to treat in such circumstances is both legal and ethical. There *are* limits to such protection, however.
- One of the most common medical malpractice lawsuits currently being brought against obstetrician-gynecologists is the failure to diagnose breast cancer in premenopausal women.
- Office gynecology practitioners should evaluate the new cervical screening recommendations in light of

(continues)

their patient populations as a whole and judge the applicability for each individual patient.

- Two potential HPV vaccine liability questions remain unanswered: the first is whether clinicians who fail to counsel young women about the possibility of being vaccinated against HPV, or who fail to administer the "cancer-preventive" vaccine, and the second relates to the role of vaccination in prevention of HPV-related noncervical cancers.
- Regarding genetic screening modalities, the most critical point for the general obstetrician-gynecologist is recognizing when a patient should be referred to a center with expertise in genetic counseling and/or testing center.
- GINA modified the HIPAA privacy requirements and extended the protections provided to patients with a personal or family history of genetic disorders and prohibits discrimination by employers or health care insurers based on an individual's genetic information.
- GINA does not mandate coverage of genetic testing nor does it provide protections from discrimination in determining life, disability, or long-term care insurance.
- The use of EHR opens up entirely new areas of potential liability for office practitioners, such as (a) the failure to use EHR in the physician's office, (b) the use of EHR by the physician's office but the failure to read or review all of the information contained in the patient's EHR, and (c) unintentional or erroneous release of confidential patient information contained in the EHR.
- Providers should be mindful of their web presence; the latter includes not just the professional medical website(s) they may appear in but also the personal information and results which patients may obtain if they "Google" the physician's name or go to Facebook.
- Physicians who currently engage in Internet-based diagnosis and prescription writing should recognize that in the absence of hands-on examination, they may be open to malpractice liability.
- Individual state legislatures can and routinely do pass bills which by statute regulate some aspects of medical practice. Providers must be aware of what these statutes are in the area(s) where they practice.
- Physicians practicing office gynecology should be familiar with published clinical practice guidelines by ACOG and other relevant professional societies.
- All of the medical records kept in the office on a patient suing a physician are critical and discoverable. This includes the chart (whether paper or electronic), all hospital records, all prescription records, and any written and electronic correspondence.
- Under no set of circumstances should any written or electronic record be altered in response to being served with a complaint from a patient's attorney. An accurately dated and carefully worded and objective addendum may be added to the medical record, however.
- Although "physician apology laws" vary from state to state, it is always important to be honest about adverse events and to both acknowledge to the patient that it occurred and to provide a straightforward, honest explanation about the events which transpired.
- ACOG has proposed guidelines for the testimony content and medical qualifications of experts that are more stringent than the more relaxed standards state civil courts use to screen potential expert witnesses.

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