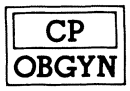

Clinical Perspectives in Obstetrics and Gynecology

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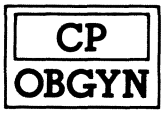

Clinical Perspectives in Obstetrics and Gynecology

perspective *noun: . . . the capacity to view subjects in their true relations or relative importance.*

Each volume in Clinical Perspectives in Obstetrics and Gynecology covers in depth a major clinical area in the health care of women. The objective is to present to the reader the pathophysiologic and biochemical basis of the condition under discussion, and to provide a scientific basis for clinical management. These volumes are not intended as "how to" books, but as a ready reference by authorities in the field.

Though the obstetrician and gynecologist may be the primary provider of health care for the female, this role is shared with family practitioners, pediatricians, medical and surgical specialists, and geriatricians. It is to all these physicians that the series is addressed.

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Pediatric and Adolescent Obstetrics and Gynecology

Edited by
J.P. Lavery · J.S. Sanfilippo

With 106 Illustrations

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New York Berlin Heidelberg Tokyo

J. Patrick Lavery, Associate Professor, Department of Obstetrics and Gynecology, Director, Division of Maternal-Fetal Medicine, University of Louisville, Medical Director, Teenage Parent Program, Louisville, Kentucky, U.S.A.

Joseph S. Sanfilippo, Associate Professor, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, Co-Director, Pediatric Adolescent Gynecology, University of Louisville, Louisville, Kentucky, U.S.A.

Series Editor: Herbert J. Buchsbaum, M.D., Department of Obstetrics and Gynecology, University of Pittsburgh—Magee Women's Hospital, Pittsburgh, Pennsylvania, U.S.A.

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To our children—Cathryn, Angela, Andrea, and Luke—
who have taught us much about pediatrics and adolescence

Contents

Preface

This book covers a broad area—the problems associated with female development—from the appearance of gender abnormalities in the delivery room, through the trials of pubescence, early maturation, and precocious childbearing.

Experts from many diverse fields of scholarship have contributed chapters covering a wide range of subjects. The contributors have concentrated on their areas of expertise. The broad range of this book is unique; no other textbook covers as many areas. The diversity of subjects covered will help the reader (gynecologist, pediatrician, nurse, health counselor, social worker, or psychologist) to understand both the physical and psychological problems which beset the female, from birth to adolescence. Because of the wealth of information presented, we hope that this volume will serve as a reference source and as a basis for further in-depth studies.

The editors wish to express sincere thanks for the efforts "above and beyond the call of duty" on the part of many members of our staff. A special thank you to Carrie Marcell R.N., our research nurse and University of Louisville coordinator for this project, for her time and effort in putting up with the vagaries of the editors; and to Betty Jones and Linda Grear for their fine secretarial work. Special recognition is due Sue Koenig, whose patience with us in adapting the text to our word processor made our job a great deal easier. Mrs. Koenig recently passed away after a short illness, we will miss her. Our further appreciation goes to the staff of Springer-Verlag for their support and cooperation in this project, and to Herbert J. Buchsbaum M.D., initial collaborator and senior editor of this series, whose thoughts, advice and encouragement enabled this project to be completed.

J. Patrick Lavery
Joseph S. Sanfilippo

Contributors

Salvatore Bertolone, M.D.
Associate Professor, Department of Pediatrics, University of Louisville, Kosair-Children's Hospital, Louisville, Kentucky, U.S.A.

John A. Carlson, M.D.
Associate Director, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

Christine L. Cook, M.D.
Associate Professor, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, University of Louisville, Louisville, Kentucky, U.S.A.

Susan M. Coupey, M.D.
Assistant Professor, Department of Pediatrics, Montefiore Medical Center/ Albert Einstein College of Medicine, Bronx, New York, U.S.A.

Frank D. DeLeon, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, Texas Tech University Medical School, Louisville, Kentucky, U.S.A.

Richard Fellows, M.D.
Clinical Associate Professor, Department of Radiology, University of Louisville, Kosair-Children's Hospital, Louisville, Kentucky, U.S.A.

Barbara Ann Fitzgerald, M.D.
Assistant Professor, Department of Psychiatry, University of Louisville, Kosair-Children's Hospital, Louisville, Kentucky, U.S.A.

Starr Gantz, R.D.
Department of Pediatrics, University of Kentucky College of Medicine, Lexington, Kentucky, U.S.A.

Alvin F. Goldfarb, M.D.
Professor of Obstetrics and Gynecology, Jefferson Medical College of Thomas

Jefferson University, Program Director of Department of Obstetrics and Gynecology, Delaware Medical Center, Newark, Delaware, U.S.A.

Donald E. Greydanus, M.D.
Director, Adolescent Medicine Program, Raymond Blank Memorial Hospital for Children, Des Moines, Iowa, and Clinical Associate Professor of Pediatrics, University of Iowa Hospitals & Clinics, Iowa City, Iowa, U.S.A.

Jay L. Grosfeld, M.D.
Professor and Director, Section of Pediatric Surgery, Indiana University School of Medicine, and Surgeon and Chief, James Whitcomb Riley Hospital for Children, Indianapolis, Indiana, U.S.A.

Arthur L. Herbst, M.D.
Joseph Bolivar Delee Distinguised Service Professor and Chairman, Department of Obstetrics and Gynecology, The University of Chicago School of Medicine, Chicago Lying-In Hospital, Chicago, Illinois, U.S.A.

Melissa L.F. Knuckles, M.D.
Division of Dermatology, Department of Medicine, University of Louisville, Louisville, Kentucky, U.S.A.

William L. Koontz, M.D.
Assistant Professor, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Louisville, Louisville, Kentucky, U.S.A.

J. Patrick Lavery, M.D.
Associate Professor, Department of Obstetrics and Gynecology, Director, Division of Maternal-Fetal Medicine, University of Louisville, Medical Director, Teenage Parent Program, Louisville, Kentucky, U.S.A.

Peter A. Lee, M.D.
Professor of Pediatrics, University of Pittsburgh, Children's Hospital, Pittsburgh, Pennsylvania, U.S.A.

John D. Looff, M.D.
Clinical Instructor, Department of Obstetrics and Gynecology, University of Kentucky College of Medicine, Lexington, Kentucky, U.S.A.

Byron J. Masterson, M.D.
Professor and Chairman, Department of Obstetrics and Gynecology, University of Louisville, Louisville, Kentucky, U.S.A.

Paul G. McDonough, M.D.
Professor, Department of Obstetrics and Gynecology, Director, Reproductive Endocrine Section, Medical College of Georgia, School of Medicine, Augusta, Georgia, U.S.A.

Elizabeth A. McGee, M.D.
Assistant Director, Center for Public Advocacy Research, New York, New York, U.S.A.

Gabe Mirkin, M.D.
Associate Clinical Professor of Pediatrics, Georgetown University, Washington, D.C., U.S.A.

Lafayette G. Owen, M.D.
Associate Professor, Chief, Division of Dermatology, Department of Medicine, University of Louisville, Louisville, Kentucky, U.S.A.

John Pietsch, M.D.
Assistant Professor, Department of Surgery, Division of Pediatric Surgery, University of Louisville, Louisville, Kentucky, U.S.A.

Richard H. Reindollar, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Genetics, Medical College of Georgia, School of Medicine, Augusta, Georgia, U.S.A.

Joseph S. Sanfilippo, M.D.
Associate Professor, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, Co-director, Pediatric Adolescent Gynecology, University of Louisville, Louisville, Kentucky, U.S.A.

Deborah S. Saunders, M.D.
Assistant Professor, Department of Pediatrics, Director, Bronx Consortium for Adolescent Health, Division of Adolescent Medicine, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York, U.S.A.

Kenneth N. Schikler, M.D.
Assistant Professor, Department of Pediatrics, Director of Adolescent Gynecology, University of Louisville, Kosair-Children's Hospital, Louisville, Kentucky, U.S.A.

Laura Schiller, B.S.
Cornell University Medical School, New York, New York, U.S.A.

G. Randolph Schrodt, Jr., M.D.
Assistant Professor, Department of Psychiatry, University of Louisville, Louisville, Kentucky, U.S.A.

Elizabeth K. Senekjian, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, The Chicago Lying-in Hospital, Chicago, Illinois, U.S.A.

Mona M. Shangold, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, Sports Gynecology Center, Georgetown University, Washington, D.C., U.S.A.

Steven R. Smith, L.L.D.
Professor of Law, University of Louisville, Louisville, Kentucky, U.S.A.

Major I. Keith Stone, M.D.
Chief of GYN Service, Department of Obstetrics & Gynecology, Madigan Army Medical Center, Tacoma, Washington, U.S.A.

Najib Wakim, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, Chief, Division of Reproductive Endocrinology and Infertility, Medical College of Ohio, Toledo, Ohio, U.S.A.

Thomas R. Weber, M.D.
Associate Professor, Department of Pediatric Surgery, St. Louis University, Cardinal Glenon Children's Hospital, St. Louis, Missouri, U.S.A.

Robert Wild, M.D.
Assistant Professor, Department of Obstetrics and Gynecology, Director, Reproductive Endocrinology and Fertility Service, Medical Director, University Reproductive Endocrinology Laboratory, University of Tennessee, Memorial Research Center and Hospital, Knoxville, Tennessee, U.S.A.

Emery Wilson, M.D.
Professor, Department of Obstetrics and Gynecology, University of Kentucky College of Medicine, Lexington, Kentucky, U.S.A.

Marvin A. Yussman, M.D.
Professor, Department of Obstetrics and Gynecology, Director, Division of Reproductive Endocrinology, University of Louisville, Louisville, Kentucky, U.S.A.

Physical Maturation 1

Susan M. Coupey and Deborah S. Saunders

A girl's late childhood and early teens are years of rapid physical changes. Between ages 10 and 15, girls grow approximately 25 cm, gain an average of 25 kg, and develop all of the secondary sexual characteristics of physiologically adult women, including the capacity to reproduce. However, while most 15-year-old girls are physically mature, the majority still are not emotionally, cognitively, and socially mature. The physical maturational changes of early adolescence are followed in the midteenage years by dramatic changes in behavior. Girls 15 to 18 often begin to explore their newly acquired sexuality; dating, petting, and sexual intercourse usually first occur in this age group. The relative psychologic and cognitive immaturity at this stage of mid-adolescence contributes to the high frequency of medical problems that result from sexual behavior. By the early 20s, psychosocial maturation begins to catch up with physical maturation, so young women this age are better equipped to make mature decisions, especially regarding their sexuality.

While the above developmental timetable represents the average maturational sequence, there is wide variation in the timing of both physical and behavioral milestones. Chronologic age in girls 9 to 17 is not specific enough for gynecologic assessment. One 12-year-old girl may be entirely prepubertal with immature genitalia that require an examination using pediatric gynecologic tehniques, whereas another the same age may be fully physiologically mature and capable of undergoing an adult pelvic examination. Yet both of these girls are entirely within the normal range of development, despite dramatically different anatomy and physiology (Fig. 1-1). Cognitive and psychosocial development do not necessarily parallel physical development, nor do they proceed at a similar rate. While these 12-year-old girls are different physically, they may be equally emotionally and cognitively immature.

Components of Physical Maturation

The components of physical maturation include statural and ponderal growth, and the development of secondary sexual characteristics and menarche. Physical maturation is influenced by various factors including heredity, social class, nutrition and physical or emotional stress.

Statural and Ponderal Growth

Skeletal Growth

From age 2 years to the onset of puberty, girls grow at the rate of approximately 5 cm per year. When puberty begins, linear growth accelerates and peaks at about 8 cm per year.[1] In the average maturing girl, this growth acceleration begins at about age 10 and reaches its peak at 12. Linear growth decelerates between ages 12 and 14 and finally ceases. Early- and late-maturing girls follow a somewhat different growth pattern, with early maturers having the highest peak height velocity (Fig. 1-2). It should also be noted that

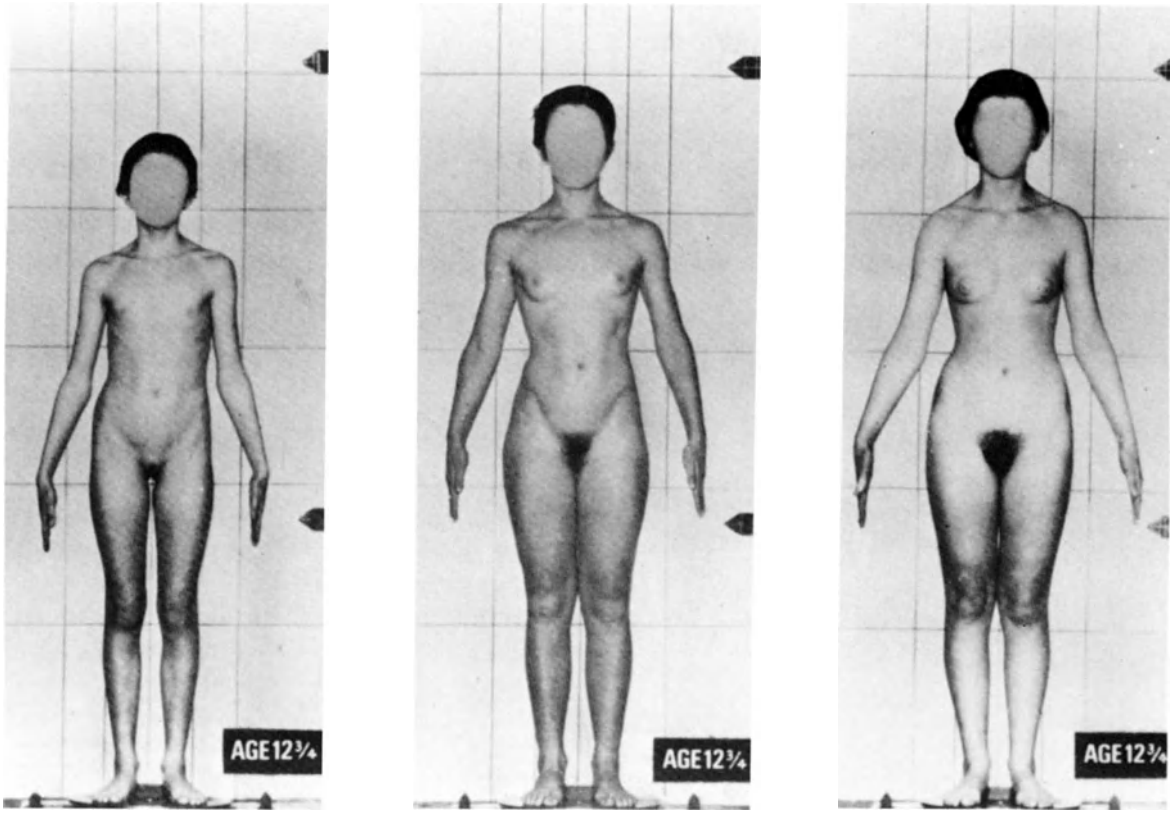

Figure 1-1. Three girls, all aged 12 3/4 years, who demonstrate the normal variability in the rate of adolescent physical growth and development. From Tanner JM, cited in Smith DW: Growth and Its Disorders. Philadelphia, Saunders, 1977. Reproduced with permission.

early-maturing girls have considerable growth potential left at menarche, whereas late maturerers usually are nearly fully grown by the time of menarche. This difference is important when considering nutritional recommendations for very young, early-maturing girls who become pregnant shortly after menarche, because the greatest maternal/fetal competition for nutrients would be expected to occur in these girls.

Serum alkaline phosphatase concentration can be used as a biochemical marker of the adolescent growth spurt. This enzyme is produced by growing bone, and the serum concentrations follow a developmental curve that can be superimposed on the height velocity curve for the individual girl.[2,3] The normal peak serum alkaline phosphatase concentration in growing girls is considerably higher than the upper normal limit for adults and care must be taken not to mistake a high value in an adolescent as representative of liver disease.

In addition to a growth spurt in height, adolescent girls have a particularly large spurt in hip width (Fig. 1-3).[4] This is the result of differential growth of the pelvic bones, and it occurs at a similar time as the height spurt. By menarche, girls have passed the peak velocity of their pelvic bone growth. As with linear growth, however, early maturers will have completed less of their pelvic growth at menarche than those who mature later.

Weight and Change in Body Composition

About 45% of the female's final adult weight is gained during adolescence. The weight gain spurt is similar to the height spurt, but it peaks about 6 months later. Thus, peak weight velocity occurs at an average age of 12.5, at approximately the time of menarche. Body

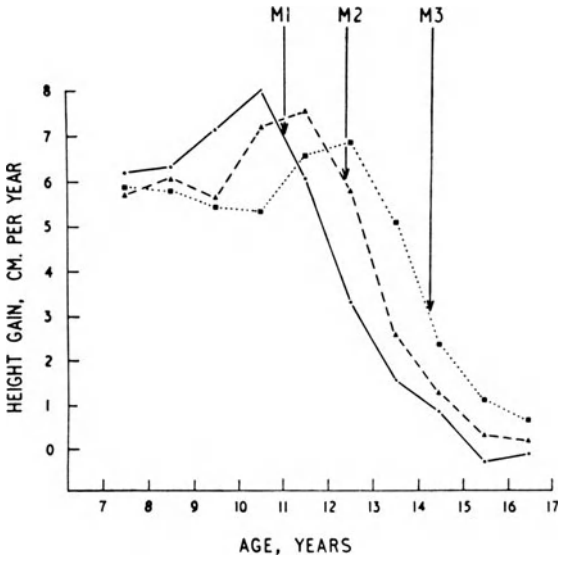

Figure 1-2. Demonstration of peak height velocities for early-, average-, and late-maturing girls, as well as the average interval between the peak height velocity and menarche (*M*). *M*1, *M*2, *M*3, average age at menarche for early, average, and late maturers, respectively. From Simmons, K. and Greulich, W.W., cited in Tanner JM: Growth at Adolescence, 2nd ed. Oxford, Blackwell Scientific, 1962. Reproduced with permission.

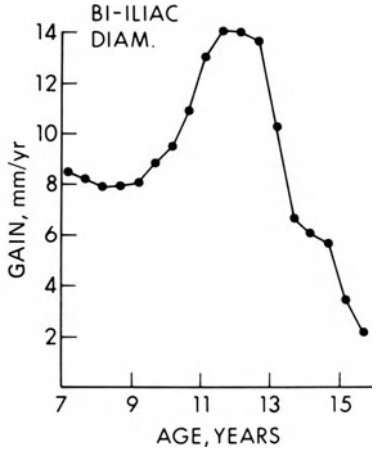

Figure 1-3. The magnitude of the rate of growth of the bi-iliac diameter in girls with peak height velocities between 12 and 13 years of age. Redrawn with permission from Tanner JM: Growth at Adolescence, 2nd ed. Oxford, Blackwell Scientific, 1962.

composition also changes during adolescence and girls become relatively fatter as they approach physical maturity.

Frisch and McArthur, in a longitudinal growth study of a large number of girls, devised curves that show percentiles of body fat by calculating the total body water as a percentage of body weight (Fig. 1-4).[6] The tenth percentile of fractional body water, 59.8%, is equivalent to about 17% body fat, which is the minimal amount of fat found clinically to be necessary for the onset of menses. Thus, girls with primary amenorrhea as a result of undernutrition must have at least the weight for height that falls on this tenth percentile line to begin menstruation.

Physiologically mature girls and women aged 16 and over who have secondary amenorrhea due to weight loss must be about 10% heavier than perimenarchial girls before menses will resume. The tenth percentile of fractional body water for mature girls and women is lower, 56.1%, reflecting less water and about 22% of body fat. This indicates the minimal degree of fat observed clinically to be necessary for the restoration and maintenance of menstrual cycles. Of course, there are other factors that influence the onset and regularity of menstrual cycles, the most notable of which is psychologic stress. Thus, even though an endocrinologically normal adolescent has the minimal degree of body fat, she still may not menstruate because of other factors.

The use of ideal weight for height is a less complex and accurate but clinically useful method of assessing the nutritional status of adolescent girls and relating it to physical maturation and menstruation. The girl's measured height and weight are plotted for her chronologic age on an appropriate growth curve (Fig. 1-5). The ideal weight is the weight for age on the same percentile as her height. In the example in Fig. 1-5, the patient's height is at the 20th percentile, so her ideal weight would be about 49 kg. The weight at which menarche occurred was 43kg, 12% below ideal. In general, menstruation does not occur in girls who are more than 15% below ideal weight for height. This method of nutritional assessment is easily done, can be readily understood by the teenager and her parents, can reinforce the need for an increased caloric intake, and can help to discourage the use of

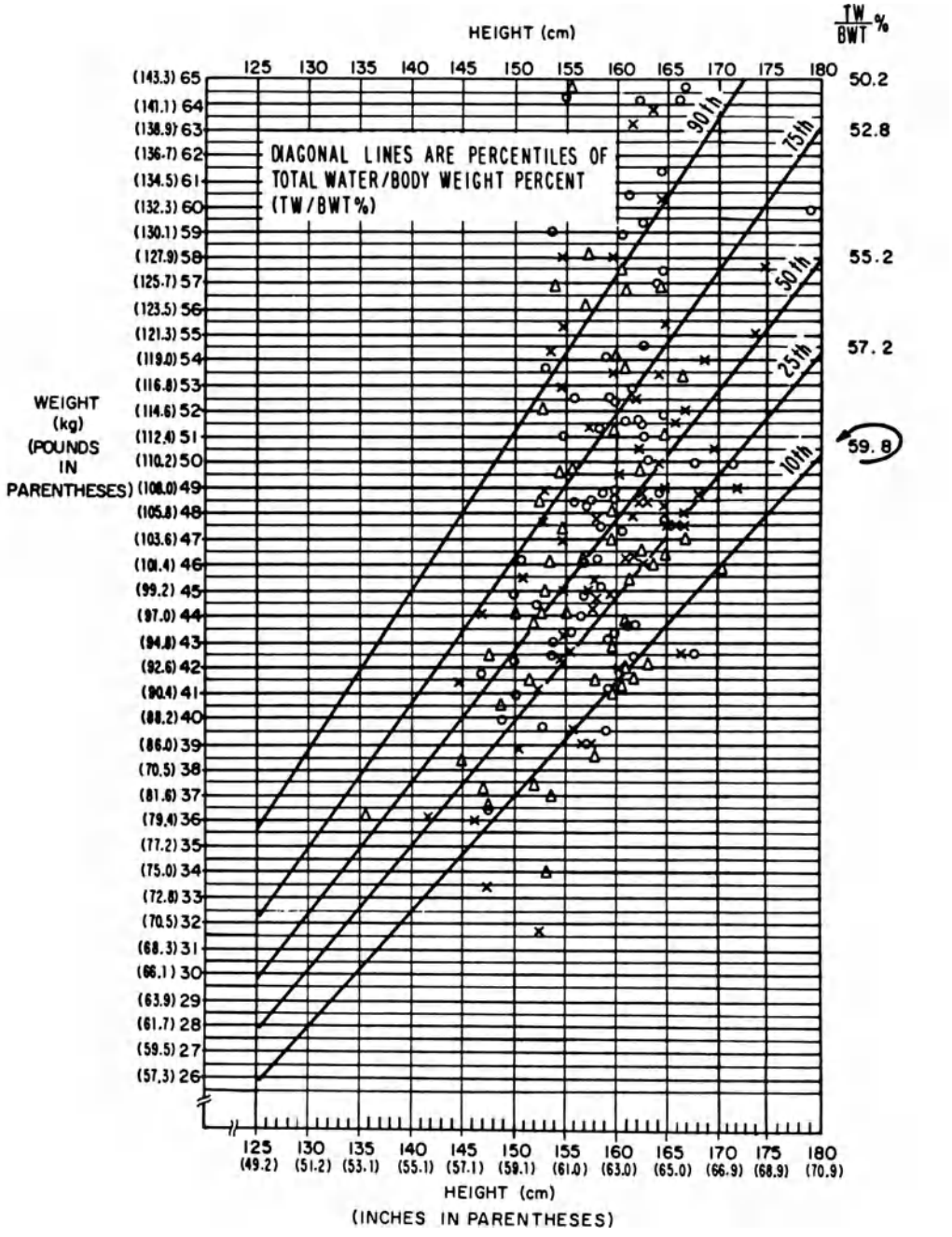

Figure 1-4. The minimal weight for height necessary for the onset of menarche is shown on the tenth percentile diagonal line as it crosses the vertical height lines. The girl's height growth must be completed or close to completion. From Frisch RE, McArthur JW: Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 185:949–951, 1974. Copyright 1974 by the American Association for the Advancement of Science. Reproduced with permission.

hormonal therapy for amenorrhea caused by malnutrition.

Development of Secondary Sexual Characteristics

Each girl's development of secondary sexual characteristics and reproductive system maturation occurs in an orderly sequence. The age at onset and the duration of these anatomic and physiologic changes vary among individuals. A standard method for measuring and classifying these changes has been described by Tanner and usually is referred to as Tanner stages 1 through 5.[7,8] Breast development, which is influenced by estrogens, and pubic hair growth, stimulated by androgenic hormones, are the two characteristics chosen by Tanner to indicate the development of the female reproductive system (Figs. 1-6 and 1-7). Other secondary sexual characteristics such as axillary hair growth, uterine fundus growth, and an increase in and redistribution of body fat are either more difficult to measure or less consistent in their development, and as such are not useful for staging.

Breast development is the first visible sign of puberty in approximately 75% of girls. Pubic hair usually appears within a few months after breast budding, although it may appear concurrently with or before breast development in some normal girls. The normal age range for breast budding is between 8 and 12; less than 1% of girls in the United States have no sign of breast development by age 13.[9] The initial appearance of pubic hair usually occurs between ages 8 and 13. The following is a description of the five Tanner stages, including both breast and pubic hair stages as well as other associated changes that are not staged but which usually occur at a similar developmental level. It should be noted that breast and pubic hair development need to be staged separately in each patient because they are not necessarily concordant.

Tanner Stage 1

There is no breast or pubic hair development. The vaginal mucosa is thin, red, and somewhat dry. This is normal for the prepubertal girl.

Tanner Stage 2

Breast buds appear, and the areolar diameter increases. The labia majora wrinkle, become more vascular, and develop hair follicles. Fine, downy pubic hair can be seen on the labia majora. The vaginal mucosa starts to become thick, pink, and moist. The uterine fundus begins to enlarge. There is a change in the distribution of body fat and the hips begin to widen. The height spurt begins. This occurs in the average girl between ages 10 and 11.

Tanner Stage 3

The breasts continue to enlarge. The small amount of pubic hair on the labia majora becomes darker, coarser, and adultlike in texture. The labia minora becomes more pendulous, the vaginal mucosa becomes thicker, and the vagina lengthens. A white vaginal discharge may appear. The fallopian tubes increase in diameter, and the uterine fundus continues to enlarge. The axillary sweat glands begin to function. The sebaceous glands of the facial skin become active and acne may appear. Most girls are now in their rapid growth phase and achieve peak height velocity during this time. The average maturing girl between ages 11 and 12 is in this developmental stage.

Tanner Stage 4

The breasts continue to enlarge, and the areola forms a mound that is separate from the rest of the breast tissue. Pubic hair covers the perineum and mons veneris but does not spread onto the thighs. The vagina and uterus continue to enlarge. Menarche occurs. Linear growth is decelerating but has not ceased. This stage occurs in the average 12- or 13-year-old girl.

Tanner Stage 5

Breasts and genitalia now are adult. Pubic hair spreads to the thighs. Ovulation begins and becomes regular. Linear growth ceases. This stage usually occurs between the ages of 13.5 and 15.

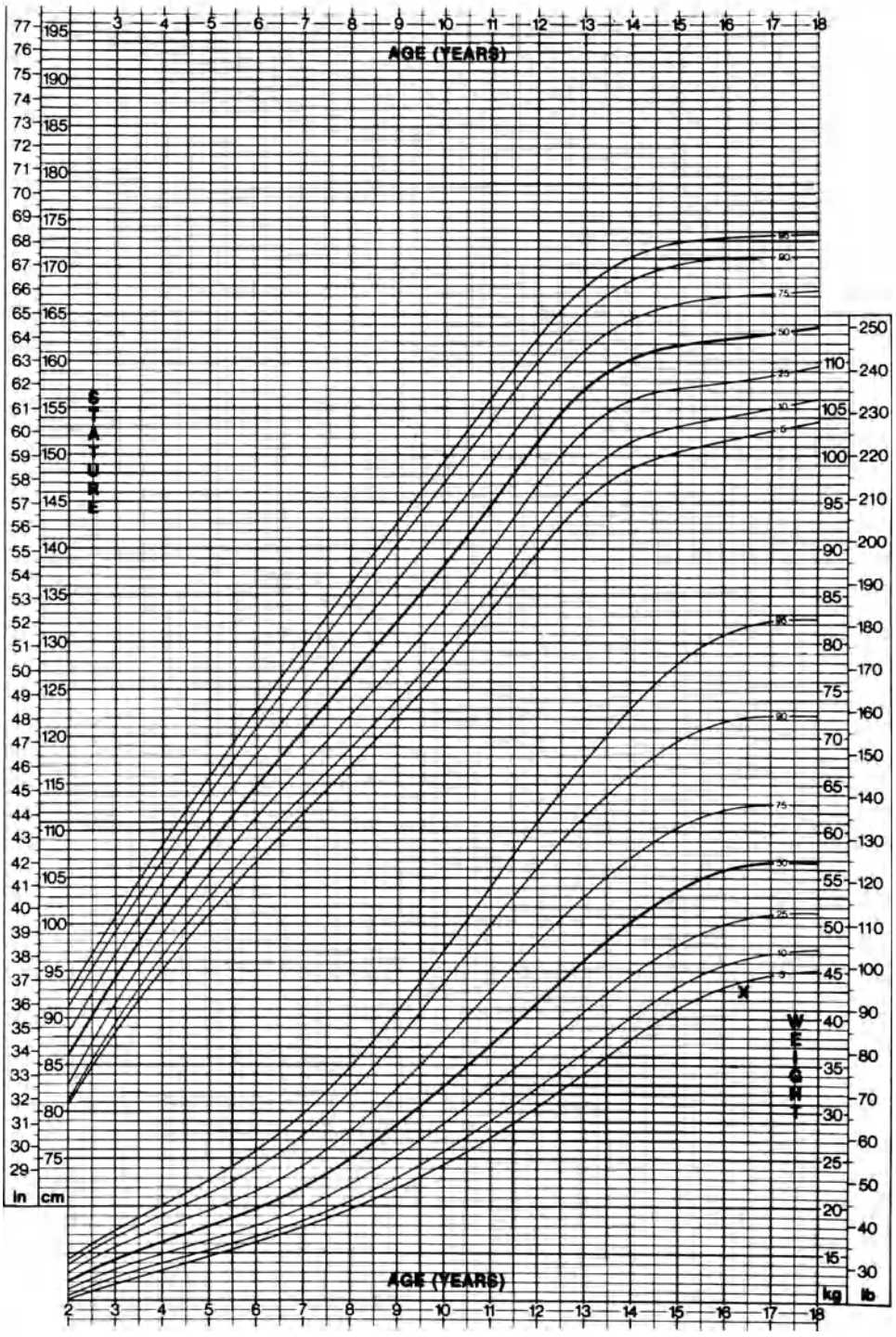

Figure 1-5. Physical growth percentiles for girls aged 2 to 18 years. Adapted from National Center for Health Statistics: NCHS Growth Charts, 1976. Copyright 1976, Ross Laboratories, Columbus, Ohio. Reproduced with permission.

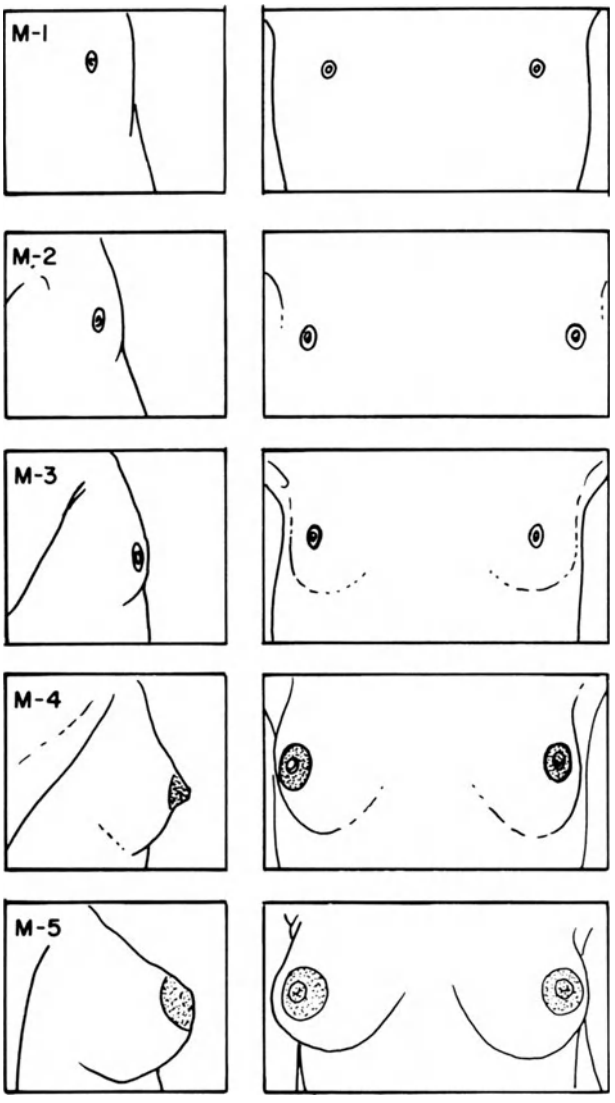

Figure 1-6. The five stages of breast development, according to Tanner and Marshall. From Van Wieringen JC, cited in Styne DM, Kaplan SL: Normal and abnormal puberty in the female. Pediatr Clin North Am 26(1): 123–148, 1979. Reproduced with permission.

Menarche

The average age at menarche in the United States is 12.6, with a range of 8.5 to 16.[10] As noted above, menarche most commonly occurs at Tanner stage 4. However, menstruation occasionally begins earlier. For example, menarche may occur in an adolescent with Tanner stage 2 breasts and stage 3 pubic hair. Menstruation does not, however, begin prior to any secondary sexual characteristic development; thus, vaginal bleeding in the prepubertal girl always is abnormal. Similarly, menstruation should begin no later than 1 year after a teenager has reached Tanner stage 5 for both breast and pubic hair development.

The onset of menses is a dramatic event that signals the possibility of fertility. However, it does not mark the end of physical maturation in adolescent girls. Breasts, pubic hair, and internal genital structures continue to mature for a year or two after menarche. Regular ovulation usually is not established for several months and in some girls as long as 3 years after the first menstrual period.[11] In general,

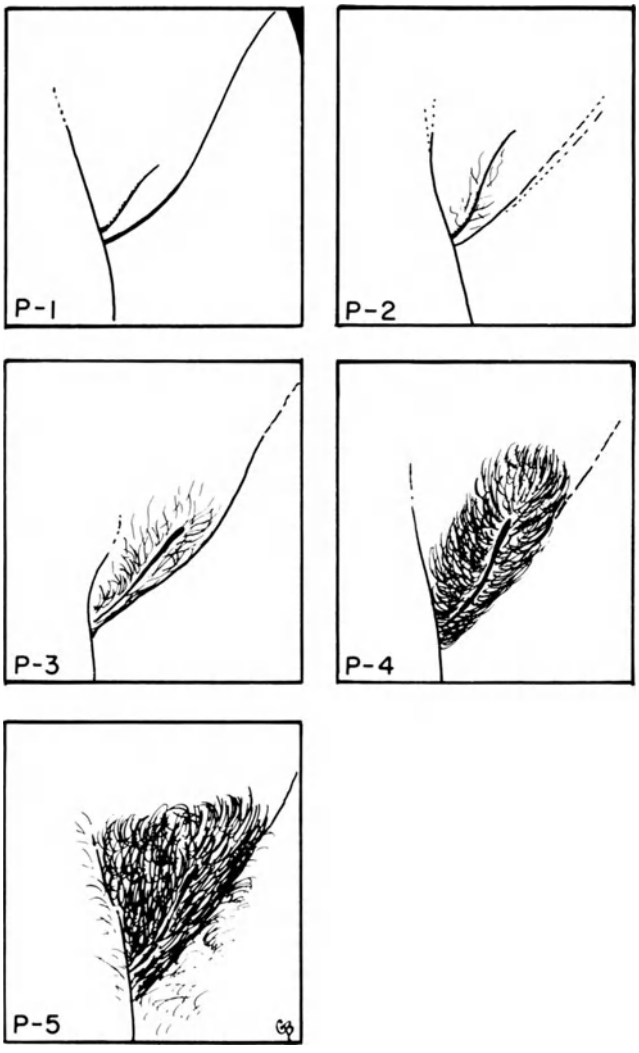

Figure 1-7. The five stages of pubic hair development in the female, according to Tanner and Marshall. From Van Wieringen JC, cited in Styne DM, Kaplan SL: Normal and abnormal puberty in the female. Pediatr Clin North Am 26(1): 123–148, Saunders, 1979. Reproduced with permission.

the girl who has her menarche at age 12.6 will be fully physiologically mature at 15.

Factors Influencing Physical Maturation

Both genetic and environmental factors influence the rate and timing of physical maturation in the adolescent. On the average, girls begin and end their adolescent physical growth and development 2 years earlier than boys.

Heredity

Heredity appears to play an important role in the chronology of physical maturation. Girls with early maturing mothers and sisters are more likely to be early maturers. The mean difference in age at menarche of 51 pairs of identical twins was 2.8 months, whereas it was 12.9 months in sisters and 18.6 months in unrelated women.[12] Early-maturing girls tend to have a more rapid and intense period of physical development, often completing their maturation in 3 years. On the other hand, late developers may take up to 6 years to mature

physically.[13] The interval between peak height velocity and menarche is about 7 months in early maturers, 12 months in average-maturing girls, and 18 months in late maturers (Fig. 1-2). Thus, both the onset and duration of physical maturation is variable and strongly influenced by heredity. The sequence of physical changes, however, remains relatively constant, with the first menstrual period almost always occurring after peak height velocity has been reached.

An additional hereditary factor that influences maturation is race or ethnicity. However, this is responsible for relatively minor variation and most previously reported racial developmental differences were, for the most part, the result of nutritional and socioeconomic circumstances. For example, in 1942 Ito showed that Japanese girls born and reared in California had their menarche an average of 18 months earlier than did Japanese girls born in California but reared in Japan.[14] This clearly demonstrates an environmental effect on maturational timing that could have been misconstrued as a racial characteristic. There are, however, some apparently real but minimal racial or ethnic differences in developmental timing. A study of delinquent youth in New York City found that the average age at menarche was 11.5 for Hispanics, 11.8 for black girls, and 12.3 years for whites.[15] Harlan et al[9] analyzed data from the United States Health Examination Survey, Cycle III, in which Tanner developmental stages for breast and pubic hair were available for a representative sample of girls between the ages of 12 an 17. Black girls appeared significantly more advanced in secondary sexual characteristic development than were their white counterparts. The difference was not attributable to socioeconomic status, geographic region, or earlier menarche because the relationships did not change when these variables were controlled. This was considered to represent a true racial difference in developmental timing.

Social Class

Social class has been shown to influence adolesent physical development in many studies. Children from the higher classes usually mature earlier and grow taller and heavier. This effect of social class reflects a complicated mixture of genetic and environmental influences. A 1950 study in Stockholm found a high correlation between parents' social class as measured by the father's occupation and children's height and weight, but very little correlation with the parents' actual net income.[16] Thus, the growth and maturational differences in the children were not simply a reflection of the economic status of the family but of the total environment. In the United States Health Examination Survey from 1966 to 1970, socioeconomic status as measured by annual income and educational level of the parents had no significant effect on adolescent development.[9] This can be interpreted as meaning that the socioeconomic status of the country has reached a level where developmental differences between rich and poor are no longer significant.

Nutrition

Among the environmental factors that influence physical growth and the timing of maturation, nutrition during childhood and at the onset of puberty appears to play a key role. In industrialized western society, the average age at menarche is approximately 3 years less than at the turn of the century.[17] This earlier menarche is associated with larger adult size and has been attributed to improved diet. Malnutrition in childhood causes growth retardation and pubertal delay. Girls in poverty-stricken third world countries have a later average age at menarche than that of North American girls (e.g., age 15.7 in Bangladesh compared with 12.6 in the United States).[10,18] Even the poorest children in North America rarely have this degree of malnutrition. However, it is found with some frequency in malabsorption syndromes such as Crohn's disease, and in anorexia nervosa. The latter condition is a common cause of severe malnutrition that is associated with pubertal arrest or delay in girls from developed nations.

Exercise, Stress, and Physical Illness

Other environmental factors that affect the timing of physical maturation include exer-

cise, psychologic stress, and major physical illness. Several recent studies have documented that rigorous physical training for sports such as gymnastics, cross-country running, swimming, and ballet dancing is associated with pubertal delay and menstrual dysfunction. Frisch et al estimated that each year of rigorous training prior to puberty delays menarche by 5 months.[19] Many girls who are amenorrheic during training have a menstrual period within a few weeks after discontinuing the exercise, despite no significant change in body composition. This suggests an independent effect of exercise on menstrual function (see Chapter 24).

Severe psychologic stress has been associated with growth failure in children, and even lesser degrees of stress such as going away to camp or college are associated with menstrual irregularities in some adolescent girls. The menstrual periods of girls with anorexia nervosa sometimes cease prior to any significant weight loss and do not resume with adequate weight gain. In these cases, resumption of menses is associated with psychologic improvement and psychologic stress is assumed to be the major cause of the amenorrhea (see Chapter 12).

Major physical illness may influence growth and pubertal development. Girls who develop diabetes mellitus prior to puberty have a later menarche than do those who acquire the disease later.[20] Delayed or arrested pubertal development may be the presenting sign of a major illness such as inflammatory bowel disease or chronic renal failure. Girls with myelodysplasia or intracranial lesions often have accelerated pubertal development and early menarche.[21] The mechanisms for the effect of an illness upon physical maturation vary depending upon the illness but may include energy wasting, poor energy intake, and psychologic stress.

Clinical Use of Physical Maturational Staging

The following case studies illustrate the clinical usefulness of physical maturational staging in the differential diagnosis of gynecologic symptoms in adolescents.

Case #1

A girl aged 15.7 years presented with primary amenorrhea. She had no significant past or present illness and was at the 60th percentile for her age for both height and weight. Her mother reached menarche at 14. The patient had begun breast development at 12, the upper limit of the normal range for this characteristic. She grew rapidly between 12 and 14 and had only grown about 1 inch during the previous year. Therefore, she probably reached her peak height velocity at about 13.5, 1.5 years later than average, an indication that she was a late developer. This girl would be expected to have her first menstrual period at about age 15 or 18 months after reaching peak height velocity (Fig 1-2). Physical examination revealed no significant abnormalities. Her breasts were Tanner stage 4 and her pubic hair Tanner stage 5. She was virginal and a speculum examination was not performed. However, a bimanual examination revealed a small, mid-puberal-sized uterus with a fundus to cervix ratio of about 2:1. It was concluded that this girl was a normal late maturer in the final stages of puberty with no evidence of anatomic or endocrine pathology. Her menarche occurred 3 months later, 1 week after she turned 16.

Case #2

A 16.2-year-old girl presented with primary amenorrhea. However, this patient also complained of fatigue and weight loss ever since an episode of "the flu" 5 months before. A family member suspected anorexia nervosa. The patient's mother had been a late developer and had her menarche at 15.5. This teenager reported noticing pubic hair at about age 13.5 and some beginning breast development at the same age. She grew 2 inches from 15 to 16, an average growth rate and about half that usually achieved at peak height velocity. Her breasts had not increased in size in the past 2 years. She had none of the psychologic features of anorexia nervosa. Her height was at the 20th percentile for her age but her weight was considerably below the fifth percentile (Fig. 1-5). She had Tanner stage 2 breasts and Tanner stage 3 pubic hair. This represents significantly late development (only 0.2% of American girls aged 15 to 17 are at this stage). External genitalia were normal and no other physical abnormalities were noted. She seemed to have begun puberty normally, but her development should have progressed beyond peak height velocity and to Tanner stage 4 breasts and pubic hair. It was concluded that this later maturer had an arrest in her pubertal development probably related to weight loss. Biochemical and radiographic studies revealed Crohn's disease. Three months after pred-

nisone and dietary therapy, she had her first menstrual period at age 16.5, exactly 4 weeks after she had reached the weight for height as determined by Frisch and McArthur to be the minimal for menstrual onset (Fig. 1-6).

Summary

Adolescent girls undergo a period of rapid statural and ponderal growth, the development of secondary sexual characteristics, and the maturation of the reproductive system. The sequence of these events is relatively constant but the onset and duration are quite variable. Thus, the anatomy and physiology may be very different among girls of the same chronologic age. A good clinical description of adolescent girls should include not only chronologic age but also height and weight percentiles, Tanner stages of breast and pubic hair development and menarchal status. A knowledge of developmental norms and factors that affect physical development is essential for the clinician who treats gynecologic disorders in adolescents.

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Neuroendocrine Maturation 2

Peter A. Lee

The concept of puberty as a threshold event at which time a switch turns on hormonal secretion resulting in the onset of maturation of sexual and reproductive function is no longer tenable. Hormonal secretion is not negligible until the age of puberty. It is apparent that there is a dramatic, dynamic ongoing maturational process involving a changing equilibrium between stimulatory and inhibitory factors regulating development which is appropriate for age throughout childhood.[1-3] The net influences responsible for this change primarily reside within the central nervous system (CNS). These are expressed by intermittent gonadotropin releasing hormone (GNRH) secretion resulting in intermittent luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, which in turn stimulate gonadal secretion. One can theorize that the underlying pattern of such secretion is regulated by a CNS oscillator which is influenced by multiple factors, including gonadal sex steroid secretion. Such an oscillator may well begin function during fetal life, be active in the neonatal period, become restrained during prepubertal childhood years, and progressively acquire mature function throughout puberty.

Thus, puberty represents the resurgence of the intermittent gonadotropin secretion which first develops and functions during fetal and neonatal life. The central nervous system, rather than gonadal function, is responsible for this reactivation as well as the quiescence during childhood years.

The theory of a gonadostat which undergoes a decrease in sensitivity to sex hormone negative feedback resulting in a turning up of hormonal synthesis and secretion, and thus the initiation of puberty, is inadequate and must be modified. This modification involves a recognition of the complexcity of controlling factors so that the low levels of gonadotropins secreted in midchildhood years are not primarily because of extreme sensitivity to the minimal gonadal sex steroid secretion, but are the result of an intrinsic CNS system which results in less gonadotropin secretion during this period even in individuals lacking gonadal secretion.[4] Thus, pubertal development results from relative changes in CNS inhibitory and stimulatory influences upon GNRH and consequently LH and FSH. The apparent change in feedback sensitivity then, at least in part, should be viewed as the result of more powerful cumulative stimulatory influences from the CNS requiring more feedback for suppression.

During fetal life, there is significant GNRH, LH, and FSH secretion (Fig. 2-1). There is evidence that this secretion can be influenced by negative feedback of sex steroids. Such feedback may account for differences in pituitary and plasma gonadotropin levels between the sexes, the lower levels found among male fetuses resulting from a greater negative feedback effect of the markedly greater and earlier sex steroid production and secretion by the fetal testes. During the latter part of gestation, the general pattern of gonadotropin secretion drops, probably as a result of maturing of the feedback mechanism responding to the high

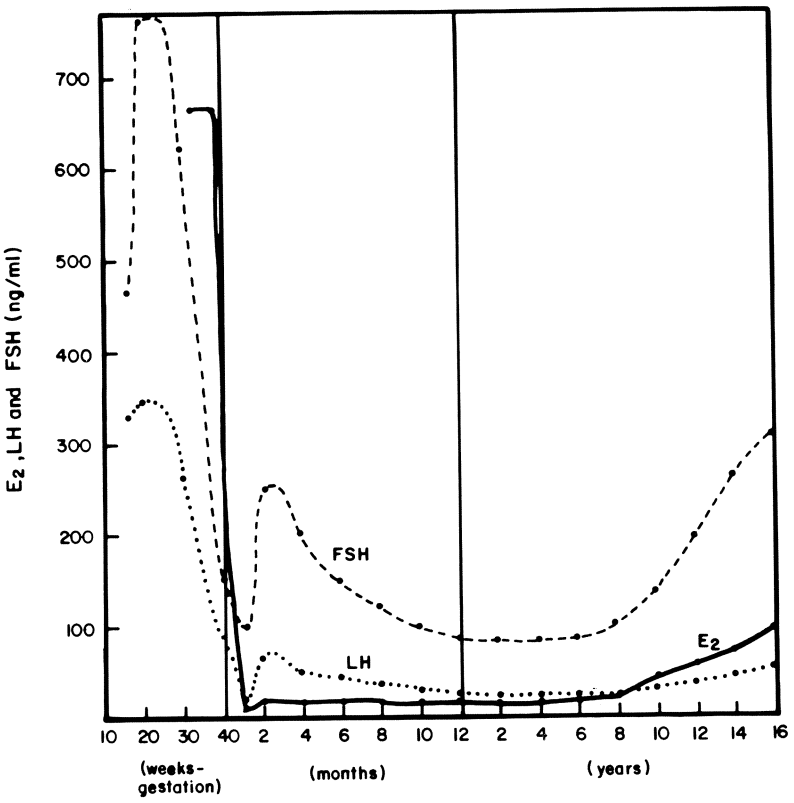

Figure 2-1. Circulating levels of FSH, LH and estradiol in relation to age. Data compiled from refs. 7, 9, 14, 21, 22, 24, 28, 73 and unpublished observations.

circulating levels of sex steroids of fetal and placental origin. After birth and after an abrupt rise and fall of LH and FSH associated with that event and accompanied by a similar phenomenon involving other pituitary hormones, LH and FSH levels gradually rise over the next several weeks, followed by a rise of sex steroids of apparent gonadal source. This rise is more dramatic for testosterone in males than estradiol in females. Nonetheless, it indicates the aggregate of influences which can be viewed as a less sensitive gonadostat. Subsequently, hormone levels fall with the lowest levels occurring at about age 6, the time when the gonadostat can be considered to be most sensitive (Fig. 2-1). This pattern of falling gonadotropin levels occurs, however, even in the absence of gonadal sex steroid secretion (agonadal individuals); hence, the driving force of the adjusted secretion is primarily CNS mediated and controlled.[4]

During late childhood, the profile shifts from a progressive fall in circulating levels to a rise (Fig. 2-1), this change reflecting a decrease in inhibitory influences or an increase in stimulatory factors or both. This results in an increase in the episodic secretion of GNRH with an increased responsiveness of LH and FSH secretion, the latter due at least in part to the self-priming effect of more regular and intense episodic GNRH stimulation. Thus, the stimulus for pubertal change resides within the CNS via a decrease in the inhibition which is independent of gonadal steroid feedback since the increased release occurs in the absence of gonads.[4] The gonads respond to the increased gonadotropin stimulation with increased sex steroid secretion. This maturation results in physical puberty, a progressive rise in gonadotropin levels, and a resultant parallel rise of sex steroid levels. The whole process is the consequence of a progressively stronger net stimulatory effect within the CNS which can be viewed as a shifting, maturing gonadostat, if one considers the gonadostat as reflective of the total input influences affecting

GNRH, LH, and FSH secretion resulting in decreased sensitivity to gonadal secretion. The process in the female is mature when a positive feedback dynamic becomes a part of the feedback scheme, so that regular cycling involving phases of negative and positive feedback occurs. It is not clear that the potential to release a surge of gonadotropins is a specific female property; rather, it may be a result of the influence of the particular hormonal milieu which does not occur in normal male physiology.

Fetal Hypothalamic-Pituitary-Ovarian Development

Gonadotropin releasing hormone (GNRH) is detectable in the hypothalamus of the 8- to 10-week-old fetus.[5,6] Thus, GNRH is demonstrable before or simultaneously with the observation of pituitary LH and FSH.[7-9] The fetal pituitary can release LH and FSH in response to GNRH as early as 10 weeks of gestation.[10] This suggests that pituitary gonadotropin production may be under hypothalamic control from the beginning. If so, however, the GNRH reaches the pituitary by another route than a developed hypophyseal portal system since the primary plexus of this system is not formed until about 14 weeks.[11] The quantity of hypothalamic GNRH increases from the time of detection until past midgestation, and this rise parallels a concomitant rise in LH and FSH secretion.[7,9,12] A study which measured GNRH content in the hypothalamus[13] found differences based on the sex of the fetus and the stage of gestation. In the female fetus peak levels, which were significantly greater than levels in the male fetus, occurred from 22 to 25 weeks of gestation.

Pituitary concentrations of FSH peak from 20 to 23 weeks of gestation, levels in pituitaries of female fetuses being greater than those from male fetuses. Plasma FSH levels in female fetuses are also significantly higher than those from male fetuses until the last few weeks of pregnancy.[7-9] FSH levels in fetal plasma from females begin to decline at about 28 weeks (Fig. 2-1) and after 34 weeks are not different from those found in male plasma. Pituitary fetal LH is also greater in the female than the male, whereas plasma levels do not differ significantly.[7-9,12] These differences in hypothalamic GNRH and pituitary and plasma LH and FSH content may be related to fetal testicular function and the effect of significantly greater testosterone levels on the development and function of the fetal hypothalamic-pituitary unit. It has not been clearly demonstrated whether this effect influences only synthesis and secretion at this stage or whether the androgen affects the differentiation and functioning potential of the exposed pituitary and hypothalamus.

Fetal gonadotropins, while not producing a dramatic steroidogenesis in the ovary similar to that occurring in the male, nonetheless may stimulate some sex steroid production. While most sex hormones in the female fetus are of placental origin, the fetal ovary does secrete some estrogen,[14,15] progesterone,[16] and androgen.[17] Such secretion is apparently unnecessary for female internal and external genital differentiation, however. Gonadotropin may be necessary for germ cell division and the development of follicles in the ovary, and hence for normal ovarian development.[18] There is a temporal relationship between FSH levels and germ cell division. Mitotic division of germ cells in the developing ovary begins during the sixth week, proceeds more actively during the second and third month, and continues until 20 to 24 weeks. Prior to this time, some oogonia begin meiotic division producing oocytes. Oocytes become surrounded by granulosa cells and primary follicles are formed. These may be identified by 6 months, and by 7 months antral follicles are present.[19] This process is inadequately developed in anencephalic fetuses who have gonadotropin-deprived ovaries.[20] Hence, gonadotropins appear to be necessary for normal ovarian development in utero.

Development During Infancy and Childhood

Gonadotropin and sex steroid levels in neonatal circulation of both females and males fall progressively during the first few days of life.[12] However, beginning about the fifth day of life, gonadotropin levels begin to rise (Fig. 2-1). The timing of this gonadotropin rise

coincides with the postnatal drop of estrogen levels due to the cessation of the placental source. This is evidence of an operative negative feedback dynamic at this age in both sexes. During the next several months and peaking at 2 to 3 months, the female infant maintains circulating LH and FSH levels higher than in subsequnt childhood years.[21-23] During this postnatal period and the subsequent several years of life, mean plasma LH and FSH levels are higher in females than males, with significantly greater FSH levels demonstrated in some studies for up to 4 years and greater LH levels up to 2 years.[22,24-26]

Coincident with the increased circulating gonadotropin levels during early infancy, estradiol levels also rise detectably. After the first 5 days of life, plasma estradiol concentrations are highest during the first to third months of life and higher during the first year of life than during later childhood,[21,27,28] suggesting greater ovarian function at this age in response to higher gonadotropin levels. Microscopic studies indicate that the ovaries actively respond to this hormonal environment at this age.[29] A greater number of preantral and antral follicles are seen. Overall ovarian size increases. Hormone profiles suggest a different setpoint of the hypothalamic-pituitary-gonadal feedback in early infancy than later in childhood. This difference is probably due to greater pituitary stimulation of steroidogenesis and the subsequent waning due to a CNS differentiation resulting in down regulation of stimulation of LH and FSH release as well as sex steroid suppression. Evidence of the ovarian effect suppressing gonadotropin secretion during infancy and early childhood is seen in the fact that the pattern of fall in gonadotropin levels is not observed until much later in agonadal children.[4,30,31] Levels in these children at this time may be in the range found in postpubertal castrated individuals.

In normal individuals, the fall of LH and FSH levels is not due to increased circulating sex steroids. This fall may in part be due to increased sensitivity of the hypothalamus to circulating levels due to changes in receptors or differentiation of CNS neuropathways resulting in more specific and localized inhibitory influences. Part of this change, however, is CNS maturation independent of gonadal steroid production, because of the demonstrable fall of very high gonadotropin levels to levels slightly above normal for age by age 6 and for a few years thereafter among individuals lacking gonads and thus gonadal steroid secretion.[4,30,32]

Although circulating gonadotropins are the lowest at age 6 or 7 years, levels are not completely suppressed, and FSH levels persist at a relatively higher level than LH during this period (Fig. 2-1). As noted above, levels are lower than in agonadal children. There are significant sex differences that could be explained by differences in feedback rather than different CNS sex differentiation due to prior imprinting, although both may occur. Specifically, the reason that girls during childhood ages have greater FSH responsiveness to GNRH[33,34] may be because males have greater feedback inhibition of FSH, perhaps via inhibin secretion by the seminiferous tubules.[35]

The demonstration of a dramatic periodic and episodic release of gonadotropin, particularly LH among adults,[36-38] with the demonstration of this pattern first occurring at the beginning of puberty during sleep (Fig. 2-2),[39,40] led to the question of whether puberty results from the establishment of an episodic release or an increased amplitude of a preexisting episodic release pattern. Subsequent studies indicate the latter to be true. The prepubertal child has been shown to have a pulsatile secretion of LH with greater mean nocturnal concentrations.[41-46] This pulsatile release during childhood can also be viewed as evidence of an oscillator functional before the onset of puberty. This pattern is more difficult to demonstrate in childhood for FSH because of the prolonged half-life dampening fluctuations, although sleep or nocturnal concentrations are greater.[47] Increased urinary excretion of not only LH but FSH verifies this sleep–waking pattern.[48]

Studies based on urinary excretion of GNRH, LH, and FSH during prepubertal years have also indicated that GNRH rises gradually and is correlated positively with LH and FSH.[49] One study found no significant differences in secretion for sex, although a subsequent study reported significantly greater levels in prepubertal boys than girls.[50]

During the second half of the first decade of life, the ovary undergoes ongoing growth and

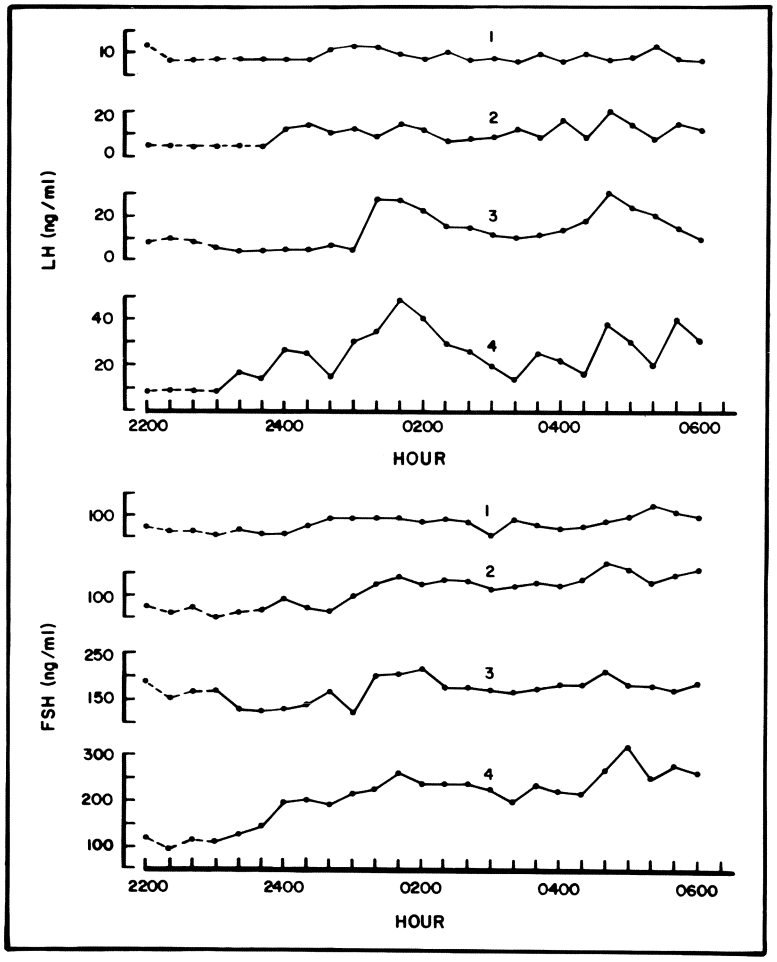

Figure 2-2. Circulating levels of LH and FSH during the night in four females. Dashed lines indicate an awake state; solid lines indicate sleep. Patient #1 was aged 7 years and prepubertal; she had minimal fluctuations of gonadotropin levels. Patient #2 had delayed puberty; skeletal age was 10 years and chronologic age 12. Patient #3 was clinically prepubertal, had a bone age of 10 and was 13 years old, and had previously been chronically ill. Patient #4 had early pubertal development and was 10 years old. These four examples show successively more mature LH and FSH patterns with higher mean levels and more episodic release. Unpublished data from the Endocrine Clinic, Children's Hospital of Pittsburgh. Supported by PHS Grant RR84.

maturation.[29] There is continual follicular growth and regression with a greater number of all stages of antral follicles, with the number of large antral follicles increasing severalfold during this period.

General Factors in Pubertal Maturation

Puberty then involves a shift of the already present, functioning, multifaceted physiology involving GNRH, LH, and FSH secretion which occurs in an episodic fashion. The key function can be viewed as the intermittent (every 90 minutes) pattern of GNRH secretion generated by a neural oscillator in the region of the arcuate nucleus of the medial basal hypothalamus. This pattern in turn regulates the periodicity of gonadotropin secretion which in turn regulates adult ovarian activity. This shift appears to involve primarily further and impressive CNS maturation and can be correlated with a variety of other factors which may be causative, resultant, or coincidental. One of these factors is the increase in GNRH receptors in the pituitary.[51] CNS maturation clearly results in stronger stimulation for

episodic gonadotropin release. Whether this is primarily due to more forceful stimuli, a marked reduction of inhibition, or a new balance of these two factors is unknown. The result is a shift in the setpoint of feedback (gonadostat) so greater quantities of sex steroids are required to suppress gonadotropin levels. Hence, one could visualize the gonadostat not as a controlling center within the brain or hypothalamus, but as a summation of the input influences that result in GNRH release and in turn LH and FSH release. The results could be visualized as a reflection of decreased restraint of the GNRH oscillator which requires more sex steroid for feedback inhibition without implying any obligatory role of sex steroids adjusting that feedback setpoint.

For years speculation concerning inhibitory influences has involved the pineal gland because of the early pubertal development which may occur when there are pathologic changes in this gland during childhood.[52] Because the pineal is known to secrete melatonin, it has been included as a possible inhibitory substance. Significantly lower serum daytime melatonin levels have been reported in pubertal boys when compared with prepubertal boys[53] but not verified by a subsequent study which failed to demonstrate any changes in daytime plasma melatonin levels in a large number of prepubertal and pubertal males and females.[54] Another study found similar 24-hour profiles of plasma melatonin in stage I (prepubertal) males aged 9 to 13 and stage III (midpubertal) males aged 13 to 15.[55] Further, the daily urinary excretion of conjugated 6-hydroxymelatonin, a metabolite of the pineal hormone melatonin, has been demonstrated not to be correlated with age from 3 to 16.[56]

However, a study of circulating melatonin obtained at night reports a striking decrease in melatonin synthesis with increasing age during childhood and adolescence. Melatonin levels at nigh were highest in children aged 1 to 5, and decreased steadily until the end of puberty when values were one-quarter those in early childhood. In contrast, daytime concentrations were uniformly low and unrelated to age.[57] Previous studies had not compared night levels in children in the early childhood years. These latter data are consistent with a hypothesis of shifting influences throughout childhood years and a decreasing inhibitory influence over time. Melatonin could be an inhibitory influence which decreases over time and results in increased GNRH secretion and puberty. If so, this is yet to be demonstrated.

There are little specific data indicating the role of neurotransmitters in gonadotropin secretion. However, effects of endogenous opioid peptides have been demonstrated. Antagonism of endogenous opiates by naloxone results in increased gonadotropin levels in adults,[58] whereas enkephalin analog administration results in decreased levels.[59] The role of opiates in childhood and early puberty has not been demonstrated. The effect of opiate antagonism has first been shown to be detectable during puberty,[60,61] but not during late prepuberty or early puberty. However, in a pubertal male naloxone has been shown to produce an increase in plasma LH pulsatile secretion, thereby suggesting an effect at the hypothalamic level.[61] Dopamine also has a suggested inhibitory effect on gonadotropin secretion.[62,63] Whether effects of dopamine and opioids exist in younger individuals but have not yet been demonstrated because of low secretory levels and infrequent low amplitude pulses is unknown.

Nutritional status is generally related to pubertal maturation and reflected by body mass and composition. These latter factors correlate with events reflecting pubertal maturation more closely than height or chronologic age. This information has led to much speculation concerning the relationship of pubertal maturation, particularly menarche, and the effect of body mass, or composition upon metabolic changes resulting in alteration of feedback sensitivity.[64-68] Although a relationship exists between body composition and pubertal events, a cause or effect relationship with gonadotropins and sex steroids is unclear and therefore this hypothesis is useful only in a general sense. It is apparent that nutritional or body weight status may be less than optimal and pubertal development delayed or stopped because of lack of availability of sufficient foodstuffs, increased requirement, or inadequate utilization because of chronic disease. Psychiatric illness may result in a deficit in nutrition and lack of pubertal hormonal maturation or reversion to a prepubertal hypogonad-like state may be a con-

sequence of that malnourished state.[69] Excessive exercise with excessive utilization of energy similarly interferes with pubertal progression.[70] Such factors suggest that pubertal and adult gonadotropin secretion may regress not because of lack of CNS maturation but as an adaptation to environmental events. This adaptation appears to be due to a change in endogenous opioid peptides since nocturnal sleep-related increase in LH secretion has been shown to occur only during opiate antagonism in such a patient.[61]

These are other factors which affect or are related to the onset of pubertal hormonal maturation. These include hyper- or hypothyroid states, growth hormone deficiency, and increased sex steroid secretion as occurs in forms of pseudosexual precocity and the congenital adrenal hyperplasias. The mechanisms whereby these factors affect brain maturation are unknown. These effects can, however, be monitored by skeletal age. Skeletal age reflects the degree of CNS-hypothalamic-pituitary maturation more closely than chronologic age[71] because bone maturation is affected by the variety of input factors mentioned above. Undernutrition or deficient thyroid or growth hormones delays skeletal maturation; obesity and excessive estrogen, androgens, and thyroid hormones advance bone age. Onset of puberty in females then occurs when bone age is 10.5–11 years, whether or not this coincides with chronologic age. Menarche occurs in the average girl at a bone age of about 13 years.

Physical and Hormonal Changes of Puberty

The preceding information indicated that the hypothalamic-pituitary-ovarian axis is active and maturing from early fetal life in preparation for the dynamic changes which occur at puberty resulting in reproductive capacity.

Increased circulating levels of gonadotropins and ovarian and adrenal sex steroids have been recognized for some time.[21,24,72,73] The earliest changes occur before there is any clinical evidence of puberty, the initial recognized change being an increase of dehydroepiandrosterone sulfate (DHEA-S) indicating the onset of adrenarche.

Adrenarche

Thus, the first recognized hormonal change of puberty is the increased adrenal androgen secretion known as adrenarche, resulting in the growth of sexual hair or pubarche. The development of sexual hair, pubic and axillary, can result from adrenal androgen secretion alone without a moiety of ovarian origin, based on the occurrence of these characteristics among agonadal patients such as in Turner's syndrome. Androgens also stimulate the development of sebaceous glands and apocrine sweat glands, particularly in the axilla. These effects may serve as clinical indications of adrenarche. Hormonal evidence of adrenarche may precede clinical evidence by several years. It is first detected at age 6 to 7 in females by the increase in DHEA-S with an elevation of dehydroepiandrosterone (DHA) levels occurring subsequently.[74–77] Adrenarche does not appear to be a result of gonadotropin stimulation.[78] Its occurrence is independent of endogenous FSH levels or exogenous LH administration.[79] There is no evidence that ACTH secretion changes with the onset of puberty since cortisol production for body mass remains the same. There is evidence that the change is one of alteration of the pattern of response to ACTH stimulation.[80]

Greater amounts of 17-hydroxypregnenolone are present at this age than before and more is converted to DHA proportionally than to 17-hydroxyprogesterone. This increase in DHA could reflect a change in steroidogenesis which accounts for the rise in DHEA-S as well as DHA seen with the onset of chemical adrenarche. It has been postulated that a specific pituitary–adrenal cortical androgen-stimulating hormone causes these changes. If such a hormone exists, its effect should be to stimulate the development of the zona reticularis which occurs concomitantly with increased DHA and DHEA-S synthesis.[81] It also has been theorized that the adrenal androgen may play a role in hypothalamic-pituitary-ovarian maturation of puberty. The increased adrenal androgens may have a maturing effect upon the hypothalamus or provide a substrate for ovarian steroidogenesis, but such an effect has not been clearly demonstrated.

Gonadarche

The elevation of circulating levels of FSH, LH, and estradiol at the onset of and during puberty until cycling begins is well established.[21,24,72,73] FSH rises prior to increases in LH. The increased FSH secretion may stimulate follicular growth and maturation in the ovary. These greater mean levels of LH and FSH result from increased secretion in an episodic fashion (Fig. 2-2).[40,43] The episodic pattern is an accentuation of a previous much lower, and probably more infrequent, pattern of release. The dramatic change in this pattern is first apparent in relation to sleep prior to the physical onset of puberty.[39] Episodic fluctuation of LH and FSH and augmented LH levels during sleep have also been demonstrated among pubertal-aged hypogonadal individuals, further suggesting the role of the CNS in this maturational phenomenon, independent of gonadal function.[82] With maturation this episodic release occurs throughout the 24-hour day.[83]

The responses of LH and FSH to exogenous GNRH differ between prepubertal, pubertal, and adult females (Fig. 2-3). The LH responses progressively and markedly increase with greater pubertal development, the increase of FSH being less dramatic.[4,32-34,84-86] Thus, change in the hormonal milieu at puberty results from this greater secretion of gonadotropins causing increased gonadal development and secretion. The increased LH and FSH secretion results from more GNRH stimulation; the rising pituitary responses to GNRH stimulation demonstrable with exogenously administered GNRH apparently are due primarily to the priming effect of ongoing greater GNRH stimulation.

Infusion of GNRH in adult females causes a rapid release of already synthesized stored

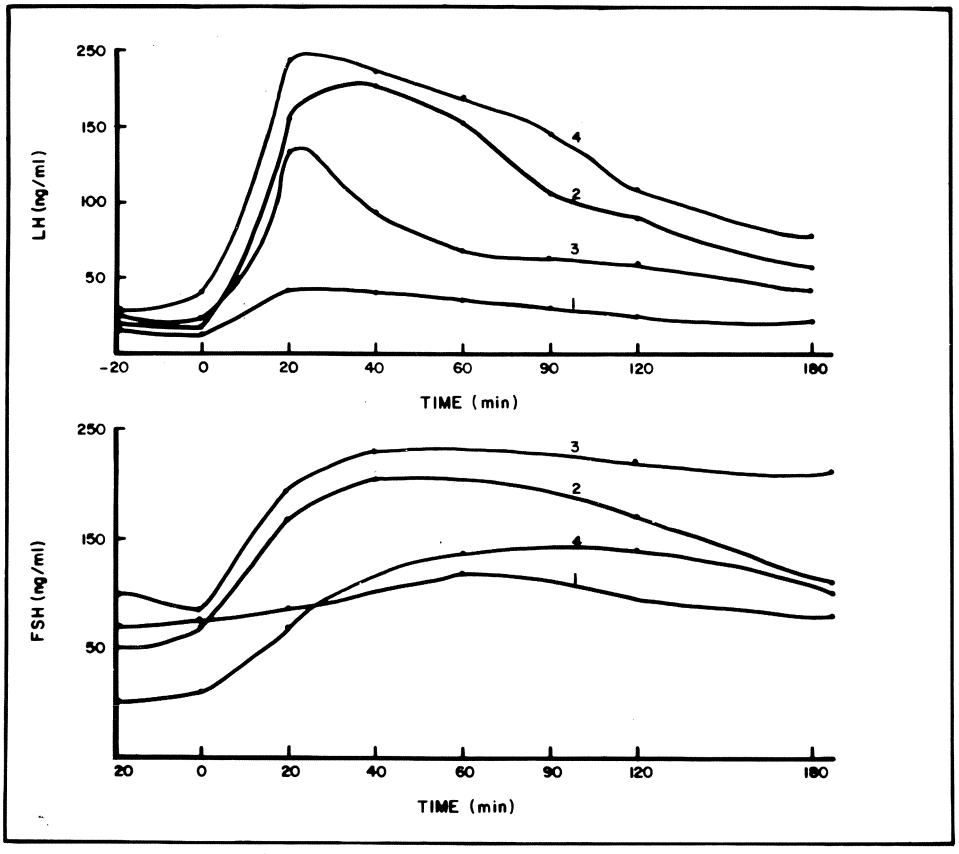

Figure 2-3. GNRH-stimulated LH and FSH responses in four girls. Numbers correspond with Tanner stage of breast development. Increased responsiveness with puberty is apparent. Unpublished data from the Endocrine Clinic, Children's Hospital of Pittsburgh. Supported by PHS Grant RR84.

gonadotropin in the pituitary and also stimulates synthesis of more gonadotropin.[87] This has given rise to the concept of two pools of gonadotropin. The portion of hormone released rapidly has been called the first pool, and that due to the presumed induced synthesis and release, the second. This pattern is consistent with the responses seen after a constant infusion of GNRH in which this two-component curve is seen in pubertal but not prepubertal children.[45] This implies a greater pituitary reserve with puberty forming an identifiable first pool plus the second pool indicating stimulated synthesis. The increased biphasic response to GNRH seems to result from increased endogenous GNRH stimulation and occurs consistently with increasing circulating gonadotropin levels indicating greater LH and FSH secretion.

The basis for the concept that the episodic pattern of LH release apparently occurs as a result of similar episodic release of GNRH with a markedly enhanced episodic pattern constituting the onset of puberty, is based upon primate studies in which puberty was induced using hourly pulses of GNRH which resulted in episodic, similarly spaced increases of LH and FSH, increased follicular development, estradiol production, menstrual bleeding, and ovulatory cycling.[88]

The administration mode (continuous or episodic) causes a considerably different effect upon gonadotropin release over time.[89] Constant infusion does not cause sustained gonadotropin secretion, whereas intermittent administration at regular intervals is followed by pulsatile release and a marked rise in circulating levels of both LH and FSH. Agonistic analogs of GNRH have been synthesized and administered in a variety of situations. These drugs are delivered so that the CNS is exposed to continuous high levels, rather than regular intermittent bursts. The characteristic response to long-term administration is an initial augmentation of gonadotropin secretion followed by a decreased responsiveness with an obliteration of episodic release and a drop of mean circulating levels.[90–93] The potential of these GNRH analogs suggests a variety of studies which can be used to evaluate pubertal physiology. To date, the most dramatic studies are the trials in the treatment of true sexual precocity.[94–96] In these patients, the episodic release of gonadotropoins is dampened or deleted, and the responses to exogenous GNRH revert to prepubertal patterns.

These findings demonstrate the cardinal role the episodic release of GNRH plays in pubertal progression and maintenance. The obliteration of episodic GNRH stimulation results in obliteration of episodic LH and FSH responses and pubertal gonadal function. The opposite is also demonstrable: pulsatile GNRH treatment in hypogonadotropic individuals due to hypothalamic but not pituitary disease results in episoidc release of LH and FSH, increase of gonadal steroids, and physical pubertal maturation (Fig. 2-4).[97,98]

Physical Development

After the detectable hormonal changes at the onset of puberty, the first physical signs of puberty occur. These may be thelarche (breast development) or growth acceleration.[73] Among most females, breast development is noticed first, although it may be after an accelerated growth rate has been present. Breast growth may begin unilaterally and proceed asymmetrically. Breast maturation, for documentation purposes, may be classified into five Tanner stages.[99] The five stages of breast development do not necessarily coincide with pubic hair development because breast development reflects estrogen stimulation and sexual hair androgen stimulation. Therefore, staging of breasts and pubic hair should be done separately (e.g., breast stage, B-3; pubic hair stage, PH2). Breast staging should be according to the following criteria: stage 1, prepubertal without palpable breast tissue, although papilla may be elevated; stage 2, a palpable and visible mound formed by breast and papilla development with increased areolar diameter; stage 3, further elevation of the entire breast; stage 4, projection of areola and papilla to form a secondary mound above the level of the general contour of breast tissue; stage 5, mature breast contour and size. This staging serves to describe progressive maturation, contour, and relative or actual areolar size but not breast size. Size, of course, differs at any stage. The time required for full maturation varies considerably[100] and is generally a reflection of amount of estrogen secretion over time. Development may be

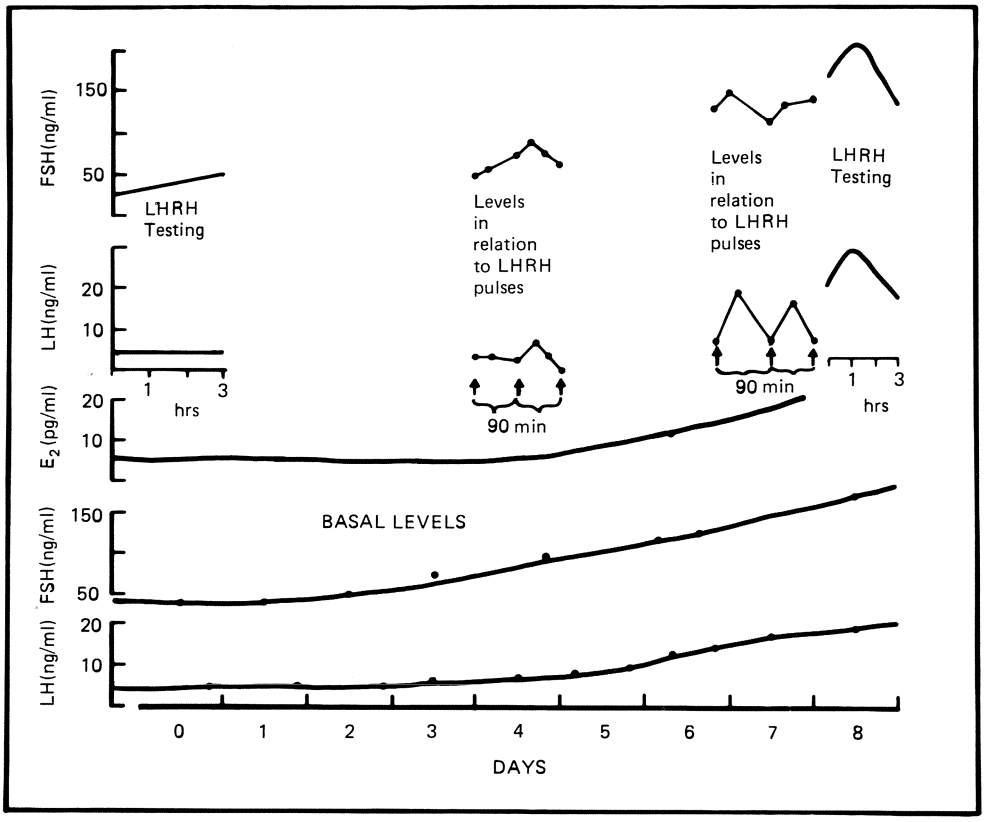

Figure 2-4. Data from the study of a hypogonadotropic adolescence girl 18 months postresection of a craniopharyngioma. The pituitary gland had been left in situ. The study involved a week of GNRH pulsatile stimulation (10 μg) every 90 minutes. The lower portion of the figure demonstrates progressive increase of basal LH, FSH, and E_2 levels to early pubertal levels. Above, GNRH stimulated (100 μg) responses on day 1 and day 8 showing change from no significant response to clear responses. Levels in relation to two pulses at 90-minute intervals are shown on day 4 and day 7 demonstrates increased responses on the latter day. Unpublished data from the Children's Hospital of Pittsburgh Clinical Research Center. Supported by PHS Grant RR84.

completed in as little as 2 years or may be prolonged as long as 8 years. In the average girl, it occurs in 3–3.5 years.

Pubic hair development reflects adrenarche, at least when it occurs as the presenting sign of puberty. When it begins, as occurs in most females, 6 months or more after breast development, androgens from both the adrenals and ovaries probably contribute to its development. Pubic hair can also be staged, based on quantity and distribution. Staging is based on the following criteria: stage 1, no pubic hair, only fine, nonpigmented hair over the pubis; stage 2, slightly pigmented straight or slightly curled hair, longer than fine prepubertal hair, usually present along labia; stage 3, greater quantity of dark, coarse, curly hair spread to the mons pubis; stage 4, adult in quality, but not extended laterally as much as in the fully developed female escutcheon; stage 5, adult in quantity and type and distributed in an inverse triangle—spread to the medial surface of the thighs, but not extended elsewhere above the base of the inverse triangle.

The rate and onset of the pubertal growth spurt among girls varies, usually beginning during or before the early pubertal stages. Pubertal growth rate is generally reflective of the degree and constancy of estrogen secretion and stimulation. The first endometrial sloughing or menarche usually is the result of a change in the pattern of estrogen stimulation. Probably menarche does not usually occur as the result of previous ovulation and corpus luteum formation, but is merely the endometrial shedding resulting from a dip in estrogen levels or sloughing of endometrial

overgrowth resulting from long-term unopposed estrogen stimulation. Because menarche may occur after varying amounts and duration of the hormonally stimulated estrogen secretion growth before menarche differs and hence the amount of growth which occurs after menarche varies considerably from 1 to 10 cm. Females who have had abundant prolonged estrogen stimulation causing considerable skeletal maturation before menstruation may grow minimally after menarche. On the other hand, females who have been exposed to fluctuations in estrogen levels causing endometrial proliferation and shedding without ovulation relatively soon after the onset of puberty can be expected to grow considerably after menarche.

The average time from onset of breast development to menarche is 2 years, although the interval may range from 1 to 6 years. Ovulation, resulting from the attainment of positive feedback, may occur before the first menstrual period but usually does not occur for months to years after the first bleeding per vaginam. Maturity of the hypothalamic-pituitary-ovarian axis is attained when a normal menstrual cycle can be accomplished.

The attainment of a normal menstrual cycle involves an intricate interplay between hypothalamic-pituitary and gonadal function which involves negative and positive feedback. The positive feedback mechanism of estrogen resulting in the midcycle surge of LH and FSH occurs with high, now low, levels of estradiol. Whether the potential for this effect is innate or results from midpubertal hypothalamic-pituitary maturation including pituitary GNRH and sex steroid receptors is unclear. The stimualtory effect of estradiol on LH and FSH has not been demonstrated in girls before or just after the onset of puberty[101] but may be present in normal males.[102] To produce a midcycle gonadotropin surge, it is apparent that the ovary must be capable of producing adequate estradiol and the pituitary reserve adequate to deliver ample gonadotropin. Estradiol inhibits gonadotropin release throughout the menstrual cycle except midcycle, although it may stimulate gonadotropin synthesis and storage.[87] However, when estradiol levels exceed 100 pg/ml for several days, positive feedback and an acute gonadotropin release ensues. This synchrony, which involves a mature follicle, results in ovulation and the potential for procreation. Puberty is then complete.

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Psychologic Maturation 3

Barbara Ann Fitzgerald

The psychologic developmental phase called adolescence begins at the onset of puberty. The basic task of adolescent maturation is to move the individual from the passive, dependent child to the independent, decision-making, sexualized adult. Although physical maturation has definite landmarks—increased height, pubic and axillary hair growth, and other alterations in physical development—psychologic maturation has no such clear markers.

Although the physical signs of puberty have changed little, the nature of adolescence has been dramatically altered over the past 75 years by a changing society. When we moved from an agrarian economy to an industrial one, our adolescents' entry into the adult world was delayed so they could have time to acquire the complex skills necessary to compete. Value systems that set limits on what is acceptable sexually and aggressively have changed, partially as a result of television. Contraceptives that are safe, inexpensive, and available to even the very young have eliminated one of the barriers to sexual intimacy—the threat of pregnancy.

However, the most significant influence on adolescent development appears to be the breakdown of the family. Long-range statistical studies reveal an increase both in the number and percentage of divorces. These same statistics show that children from divorced families have a much greater risk of becoming divorced themselves. As the rate of divorce increases, so does the number of adolescent problems. Today's increased societal pressures have influenced both the spread and progression of adolescent psychologic maturation.

Mental health professionals in the past 10 or 15 years have increasingly focused more attention on the adolescent developmental stage, probably because approximately 15% of the population is between the ages of 13 and 20. Ten percent of this group have problems requiring psychiatric intervention.

Accidents, particularly automobile accidents, are the leading cause of adolescent death.[1] The contributing influence of drug and alcohol abuse on these accidents, as well as the extent of substance abuse in the adolescent population, requires some scrutiny. In addition, suicide is the third or fourth leading cause of death in adolescents.[1]

The 7 to 10 years of adolescent development are grouped into several "phases"[2] to best illustrate the rapid and dramatic changes which occur.

Early Adolescence

The early phase of adolescence, usually beginning at 12 and ending after 14, is a period of immediate response to puberty. The youngster suddenly has strong sexual and aggressive impulses that seem to come out of nowhere and push for expression. During this early period, the adolescent clings to the family because her anxiety level is high and the family is familiar territory. Sexually, the youngster is increasingly aware that her body is maturing, and that she can "actually do it." This is frightening because the ability to relate to

others is not established to the degree that the youngster is ready or able to handle an intimate relationship with the opposite sex. Psychoanalytically, the anxiety is related to sexual attractiveness to the parent of the opposite sex. As a result of this anxiety the adolescent is increasingly modest and often avoids that parent.

This is also a stage during which the ability to deal with abstract thinking, described by Piaget's stage of formal operations, is developed and put into practice. Major characteristics of the early adolescent period as developed by the Group for Advancement of Psychiatry[3] include (1) rebellion; (2) intense narcissism and preoccupation with one's own body and self; (3) the vital importance of peer groups; (4) intense sexual urges and feelings that gain expression first in fantasies and then in masturbation and other sexual activity; (5) marked increase in aggressive urges, supported by corresponding increase in physical size; (6) marked increase in emotional and intellectual capacity with parallel broadening of interests in activities; and (7) attitudes and general behavior characterized by unpredictable changes and experimentation.

While it is said that perhaps the best thing about this phase is that it eventually ends, the psychoanalytic school has proposed that the fluidity with which one's ego structures exist during this period allows a second chance for residual conflict resolution from earlier years.

Middle Adolescence

The years 15, 16, and 17—middle adolescence—are thought to be a time of settling down. Cognitive development and intense self-absorption begin to subside and are replaced by the ability to see things more individually. Social skills are more highly developed. The paradox is that this period is usually one in which the teenager most adamantly rebels against parental values. It appears that the teenager's ego is forged by buffeting up against the parents' egos, especially the one of the same sex. Substance abuse either as a form of experimentation or rebellion peaks. Drugs or alcohol also can serve to relieve the symptoms of anxiety that plague most adolescents.

Late Adolescence

Late adolescence begins at 17 and lasts through the resolution of adolescent struggles. This is a phase that Erikson describes as identity formation.[4] The concept elaborates upon the psychologic work of weaving together and synthesizing a relatively unique, coherent psychologic self. Here, major life choices begin to be made. The adolescent chooses and tries on different types of "being" to test out the available options.

The adolescent in this phase vacillates between independence and dependence, having less contact with the parents. As the adolescent displays more emotional distance from the parents by living away or just spending less time at home, depression associated with intrapsychic or psychologic loss of the parents can occur. This loss is compensated for by more meaningful and mature relationships with peers.

Resolution of adolescence is described by the Group for Advancement of Psychiatry as being characterized by (1) separation and independence from parents; (2) the establishment of a sexual identity; (3) commitment to work; (4) development of a personal moral value systems; (5) capacity for lasting relationships and both tender and sexual love in heterosexual relationships; and (6) a return to parents in a new relationship based upon relative equality.[3]

As these tasks are continuing, adolescence sometimes seems to just fade off into young adulthood.

Female Adolescence—Special Considerations

The onset of menarche is a definite landmark in the maturational process of the female adolescent. The timing of this phase appears very important in terms of how rough the road through adolescence will be. Those girls who begin menstruating either much earlier or much later than their peers are under extreme stress. As noted earlier, identification with the peer group is important, and girls who are out of step with the group show an increase in anxiety. Moreover, the earlier-developing female is much more advanced physically than her slower-developing male peers, and thereby

usually seeks out older males who are at another developmental stage. Thus, the early-maturing adolescent female may be faced with making decisions for which she is unprepared.

Jones and Mussen in researching the timing of maturation (in particular menstruation) found that early-maturing girls tended to be relatively submissive, listless, or indifferent in social situations, as well as lacking in poise.[5] Late maturers, on the other hand, were relatively more outgoing and assured, with good leadership abilities. Peskin concluded that earlier pubertal onset was more stressful and involved a turning away from social contacts.[6] At the same time, however, these girls were less fearful and guilt-ridden about aggressive feelings than their later-maturing peers. In comparing these studies it is difficult to know which group has the advantage, the major point being that there is a difference in girls who deivate from the "norm."

Peskin also found that despite adolescent difficulties, by the time the early maturers reached 30 they were more psychologically healthy than late maturers.[6] It seems that the negative effects of early pubertal maturing do not persist and indeed can become strengths in adulthood.

Menstruation appears to enhance a girl's feelings of femininity and sexual identification, and has been understood as an organizing force around which a clearer, better-defined body image is built.[7] Adolescents' questions to their obstetrician-gynecologists or pediatricians about menstrual problems are often requests for reassurance about their "normalness." This is also true when the doctor is questioned about weight. The usual intent of this question is to find out if their figure, particularly their breast development, is normal. When adolescent girls are asked about sexual organs, breasts are usually mentioned frequently, probably because they are so visible. In interviews with 30 "normal" teenage girls, Rosenbaum found most of the concerns about their bodies centered around breasts.[8] All wanted to change some aspect, usually size. As these girls passed into later stages of development, they appeared to become less preoccupied with their bodies and more focused on their personalities.[8]

Anorexia nervosa often appears at the start of menarche. One prominent rationale in the effort to lose weight is to prevent menstruation and the development of mature body form (see Chapter 12).

Adolescent Turmoil—Is It Necessary?

For years psychiatrists have been describing adolescent development as a time of "turmoil." Extreme mood swings were understood to be the "norm" for this time of life. This made it often almost impossible to define what was "normal" in adolescent development and what was psychopathologic. Many of the suppositions about normal behavior in this group had been drawn from studies of adolescents who were in treatment. Erikson, one of the major writers in the area of development, describes adolescence as a "normative crisis."

> The final assembly of all the converging identity elements at the end of childhood (and the abandonment of the divergent ones) appears to be a formidable task: how can a stage as "abnormal" as adolescence be trusted to accomplish it? Here it is not unnecessary to call to mind again that in spite of the similarity of adolescent "symptoms" and episodes to neurotic and psychotic symptoms and episodes, adolescence is not an affliction but a normative crisis, i.e., a normal phase of increased conflict characterized by a seeming fluctuation in ego strength, and yet also by a high growth potential.[4]

Thus, Erikson suggests that we look at adolescence not as a highly disorganized time of turmoil but as a crisis that is a normal phase.[4]

Others in the field doubt that all adolescents have to have such an intense time of disruption. Offer postulates in his look at a group of normal (not in treatment) high school students that turmoil should be seen only as one route for passing through adolescence.[9] Rebellion, on the other hand, which he distinguishes from turmoil, is a prominent aspect of adolescent development. However, this does not necessarily lead to the amount of pathologic turmoil that is often described as normal. He describes three types of adolescent development, only one of which has major disruption as a component.

Offer found that development appeared to

be *continuous* in 23% of his studied teenagers.[10] These teenagers had excellent genetic and environmental backgrounds, with childhoods unmarked by the death or illness of a significant family member. The divorce rate was low and there was a low incidence of psychiatric illness. These teenagers showed steady progress through adolescence and into adulthood.

Thirty-five percent were found to have a *surgent* type of development. This pattern revealed a sequence of development that unfolded in spurts. Their genetic background was not as trouble-free as that of the continuous group. There was a higher incidence of death and divorce in their families.

Development was described as *tumultuous* in 21% of the teenagers. They had more intense turmoil and the genetic and environmental factors were less stable. There was also a marked increase in marital conflict and divorce, as well as a history of mental illness in immediate relatives. These teenagers seemed to rely more on peers, possibly because of their less stable homes. The parents of these children appeared to have greater difficulty separating from their offspring.

Therefore, Offer summarizes that turmoil in adolescent development varies in degree and type, and it is not necessarily true that all teenagers go through it with the same intensity.[9] While this is in contrast to the analytic theories of turmoil most presented by Blos[11] and Freud, evidence indicates that Offer has a valid point.

When Adolescent Turmoil Crosses the Border into Pathology

Usually it is a matter of intensity and duration that alerts one when it appears that adolescent turmoil may be degenerating into overt psychopathology. Masterson, in his study of 101 teenagers in the Paine University Clinic, found that 5 years later 60–75% of the adolescents remained impaired.[12] His conclusion was that adolescents brought for treatment were not merely benign cases of adolescent turmoil, but that psychopathology was truly present.

This raises the question of how a physician decides that an adolescent is in need of treatment. The most obvious way is by looking at the overall picture. The physician needs to consider the psychologic tasks of adolescence and determine the degree to which an adolescent has accomplished the tasks. Look at the coping capacities and the adequacy of her ability to relate to others outside the family. Reflect on the adolescent's ability for affect control within the normal range. What is her involvement in school? Is there any major disorganization in the thinking pattern? Does she exhibit any of the major symptomatology of depression or other psychiatric illness?

The physician also must try to determine the purpose of the behavior. Is it attention seeking? Is it rebellion? Is it a cover-up for other symptoms? Drug and alcohol abuse, promiscuity, and running away can all be looked upon as attention focusing, or as ways of covering up other symtoms. The physician should seriously consider making a referral for treatment when the adolescent is not functioning adequately in all or a majority of these areas.

Depression, along with anxiety, is one of the most common teenage symptoms. With suicide the third or fourth leading cause of teenage death this is a significant problem.[1] Depression may be transient, or it can be chronic, with some of the same signs and symptoms of adult depression such as decreased concentration, crying, insomnia, anorexia, and social isolation.

Sometimes the adolescent expresses the feelings of depression rather than experiences them—antisocial acting out. This includes drug and alcohol abuse, delinquent behavior, etc. The adolescent often has difficulty describing feelings, a result of a general disinclination to permit outside examination of private internal experience. Anthony postulates that relative immaturity in abstract conceptionalization contributes to this difficulty.[13] Therefore, the clinician must rely on the external surface behavior to infer the presence of affective illness.

Early schizophrenic symptoms in an adolescent are often masked. Schizophrenia involves a disintegration of the ego. But in the adolescent the ego is still forming, so it is often only over time that the definitive diagnosis can be made. One of the most common initial symptom clusters in adolescent-onset schizophrenia is social withdrawal, decreased assertiveness, concentration difficulties, and failure in school.[12]

Assessment of Adolescent Problems

Hersey, in his situational parenting concept, has attempted to assist parents and professionals in assessing of adolescents.[14,15] An element of this work is the ACHIEVE model. Each letter represents a diagnostic area to consider when evaluating problems and interventions. The following is a brief presentation of the seven areas.

A = ability. Does the child have the knowledge, skill, experience, and/or education to accomplish a specific task or tasks? If the child's problem stem from an ability deficit, the proper referral resources may well be school counseling, educational testing, vocational placement, or remedial or special education. If there are emotional problems stemming from lack of self-esteem as a result of this lack of ability, then the child may be referred to a psychiatrist, psychologist, or social worker for emotional counseling. However, the major problem in this area is lack of skill development and somehow they must be developed.

C = Clarity of objectives. Does the child's problem arise from unclear expectations, role confusion, and/or an uncertainty about family, school, or other's goals that include her? We know that unclear and unrealistic expectations are the major stress producer in both business and family life. How can these objectives be clarified? First, the source of unclarity must be identified. Then a referral for family therapy, school counseling, or psychotherapy can be made. Individual psychotherapy with psychiatrist, psychologist, or social worker would be proper only if the symptoms arise from unclarity of personal values or conflicting internal values. Basic interventions in this area mainly come from family or school counseling.

H = Help. Does the family or school provide the organizational support to assist the growth and development of the child? Do the parents provide adequate housing, nutrition, special counseling, transportation, and so on, allowing the child to use her talents to the fullest? Or is the family or school deficient in meeting these needs? Many children today suffer from a lack of appropriate organizational resources. This deficit must be dealt with before any type of counseling is feasible. Referral of the family to social/human resource programs such as public housing, ADC, Medicaid, churches, public welfare, or social organizations is appropriate.

I = Incentive. Does the child's problem originate from an unwillingness to perform tasks, as a result of a negative attitude or insecurity? The assessment of these areas is critical because insecurity denotes a growth problem, whereas negative attitude indicates a problem in relationships and values. Treatment is different in each case.

A. If the problem is negative attitude it might be appropriate for both parents and child to be present during intervention so that problem attitudes can be explored and appropriate expectations developed. Family counseling would be the primary intervention if parents were willing and able to provide the support and structure needed. Parenting education also might be necessary initially if parenting skills are too weak for the family to enter therapy together. If all communication between parent and child has been damaged, then individual therapy may be needed initially.
   1. If the negative attitude is focused at teachers or schoolwork then referral to school counseling would be indicated.
   2. If the child or parents refuse to change the negative attitude, then referral to juvenile court or out-of-home placement may be necessary. If negative parental attitude results in physical or emotional abuse, then referral to protective services is mandatory.

B. Insecurity originates from internal psychic confusion or a lack of self-esteem that forces the child to doubt herself and her abilities. This calls for individual evaluation by a mental health professional and subsequent individual or group therapy. Family interventions are possible after the child has developed a

better understanding of the problem through psychotherapy. Positive social experiences are critical for the insecure child, and placement in special educational and/or structured social groups is indicated. The growth of self is the goal of treatment.

E = Evaluation (Coaching). Does the child have the day-to-day support from family or significant others that she needs to properly grow and develop through latency and adolescence? Are parents available to provide the needed structure and to listen to the child's concerns? The lack of parental availability in our society leaves children to "go it alone" long before they are psychosocially able or willing. Parents may need to be referred for counseling and/or parenting education (e.g., situational parenting classes, parent effectiveness training). Individual therapy might be helpful in the absence of parental ability or willingness to help; group therapy also could provide support. The primary "helper(s)," however, are the parents and if at all possible they should obtain the primary counseling, as children need both positive and negative feedback.

V = Validity. Is the child functioning within the guidelines of law, moral ethics, policy, and so on? Is the child aware of breaking society's rules? Does she feel guilty? If a child has a history of antisocial, nonvalid behavior and treatment has been unsuccessful, the best referral is often juvenile court rather than psychiatric treatment. First-time offenders may do well in treatment; repeat offenders may need to see the consequences of their actions before they consider further treatment.

E = Environmental fit. What is the child's living environment, the family structure, the neighborhood, the school, the peer group? What are the supports or lack of supports and the values of the community, neighborhood, peer group, and family? In some situations out-of-home placement is the treatment of choice because of the fragmentation of the family, the composition of the peer group, the disorganization of the neighborhood, or the child's subculture. Child abuse, juvenile court, protective services, or church institutional placements are the referral agencies of choice.

Conclusion

The adolescent phase of psychologic maturation is a crucial and complex step in a process that continues throughout life. If later psychologic maturation is to proceed, the person must successfully resolve and complete the identity vs. role confusion that is an issue in adolescence.

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The Initial Gynecologic History and Physical Examination 4

Najib Wakim and Frank D. DeLeon

Discussing the initial gynecologic examination prior to and during the procedure can alleviate the anxieties and fears of the pediatric or adolescent patient and her parents. The adolescent may be reluctant and embarrassed to discuss personal matters such as sex, venereal disease, pregnancy, and contraception. Thus, it is extremely important for the physician to establish good rapport with the patient and create an environment that is as comfortable as possible.

The physician's approach to the history sets the stage for the physical examination. By gaining the trust of the patient, the physician can lessen her anxiety over the pelvic examination. The physician or other health care provider must be aware that the level of maturity may vary among girls of similar age. While a parent or guardian must be present for the history on a pediatric patient, the adolescent may be fully capable of providing her own history and indeed may prefer to do so. Thus, the approach to history taking depends upon the patient's age and maturity.

History Taking of the Pediatric Patient

A pediatric patient usually is brought to the physician's office by a concerned mother who describes the complaint. The most common reasons for consulting a physician are vaginal discharge, spotting, precocious breast development, pubic hair and/or external genitalia, or suspected sexual molestation. Less common complaints include lower abdominal pain, the possibility of a foreign body in the vagina, vulvar rashes, labial agglutination, and fear of diethylstilbestrol (DES) exposure.

Many of the aforementioned diagnoses can be quickly clarified by a gentle pelvic examination and simple laboratory tests such as vaginal smears and culture of discharge. The parent of the pediatric patient typically answers questions regarding past medical and surgical problems, medications, allergies, obstetric course, delivery, and neonatal periods, sibling and family histories, as well as developmental milestones. The parent also reviews the child's symptoms. Nevertheless, it is important to allow the pediatric patient to contribute to the history.

Vaginal spotting and discharge often are associated with a foreign body (most commonly small pieces of rolled toilet paper inadvertently lodged in the vagina). This can cause a local infection and should be investigated during the history with inquiry about past vaginal infections in family members. Although a vaginal infection can be spread by close nonsexual contact, this rarely occurs. The physician should tactfully inquire about the possibility of sexual molestation. It often is difficult to get a young patient to explain any sexual contact. Handing the child a doll and asking her to point to areas of contact often allows her to be more descriptive and less inhibited. This probably will give the physician a better idea about whether sexual molestation has taken place.

Labial agglutination occasionally is seen in the young patient and may be associated with vaginal discharge and urinary tract infection. Although the cause is unknown, the low estrogen environment may cause marked thinness of the vulvar epithelium resulting in irritation and adhesion formation of the labia. Treatment is the application of estrogen cream on the vulvar area for two weeks. Mild cases of labial agglutination may spontaneously resolve during puberty.

Signs of precocious puberty, including premature thelarche, pubarche and external genitalia development are discussed in Chapter 5.

It is crucial that the health care professional show concern and establish good rapport with his adolescent patients. Teenagers often feel insecure about the physician's attitude regarding issues as contraception, fear of pregnancy, menstrual irregularity, or simply a vaginal discharge. Adolescent patients must be given an opportunity to be interviewed alone and assured of the confidentiality of the physician-patient relationship.

A sexual history should include age at first coitus, methods of birth control used, any history of venereal disease or possible exposure, and whether dyspareunia occurs with coitus.

The subject of sexuality is a very important part of the interview. The physician should use understandable language and be neither condescending nor opinionated. This should enable the patient to volunteer questions that she might otherwise feel too embarrassed to ask. When a patient is comfortable with the physician it often becomes apparent that her initial complaint is not the real reason behind her visit. After the patient's anxiety is allayed, the physician must play detective, using subtle ways to determine why the patient is really there. Perhaps she is concerned about an unwanted pregnancy or whether she is indeed pregnant. Or maybe her complaint of vaginal discharge is merely a way of broaching the subject of contraception. It is estimated that approximately half of the 21 million teenagers in the United States are sexually active, but half of those use no contraception the first time they have intercourse.[1,2]

Part of the initial interview should be devoted to explaining the pelvic exam. This decreases the patient's anxiety. The reasons adolescents consult a gynecologist vary and include the following in order of frequency: vaginal discharge, menstrual irregularities, contraception counseling, dysmenorrhea, precocious or delayed sexual development, pregnancy determination, DES exposure, and vaginal abnormalities.

Like the interview with the pediatric patient, the teenager's interview should include questions about past medical, surgical, prenatal, family, and sibling histories. Developmental milestones are an integral part of the adolescent history. Teenage girls should be encouraged to keep a record of their menstrual periods to aid in evaluation during future visits. They also should be asked questions about any previous pregnancies and any living or dead children. Additional questions should include age of menarche, interval and duration of flow, first day of the last normal menstrual period, and last vaginal bleeding episode.

The Physical Examination

After the history, the patient should be given a brief description of the examination. This is important because this frequently is the patient's first pelvic exam; a bad experience may make her afraid of phyisicans and embarrassed by her body. If the patient is an adolescent, she should be asked if she wants her parent or guardian present during the examination. If she is a child, a parent should be in the examining room. In all cases, a nurse with special training in pediatric and adolescent gynecology is invaluable. The patient should be asked to completely undress, but should be well draped. She should not be subjected to multiple pelvic examinations because of potential psychologic trauma.

The height and weight always should be recorded and plotted on the patient's growth chart. If endocrine abnormalities are suspected, an arm span measurement is necessary and should be compared to the patient's height. The upper-to-lower ratio U/L (the length from the top of the pubic ramus to the top of the head divided by the distance from the top of the pubic ramus to the floor) also is important in such cases. "The mean U/L ratio

of white adults is 0.92 ± 0.4 (S.D.) and that of black adults is 0.85; there are no U/L ratio differences between the sexes. . . . In general, hypogonadal patients have eunuchoid proportions with a decreased U/L ratio."[1]

The skin should be inspected for any abnormalities that might reflect general systemic disease. Hair distribution (including any pubic hair) and voice pitch also should be noted because they frequently are signs of suspected endocrine abnormalities that occur with excessive androgen production. If the patient has delayed onset of puberty, any change in her ability to smell is important.

After she has emptied her bladder, the patient is placed in the lithotomy position with her feet in stirrups. Adolescents frequently feel more comfortable and are better informed if they see what the physician is doing; this can be easily achieved by using a hand-held mirror. Explaining the pelvic exam step by step or using a show-and-tell approach helps to calm the girl by making her partly responsible for the success of the examination. For example, the physician can tell the patient beforehand that when her ovaries are palpated her abdominal muscles should be relaxed. If they are not, the ovaries cannot be felt and the cause of her problem may escape notice. When the exam is actually being done, the physician should keep reminding the patient to relax her muscles, which allows adequate assessment of the fallopian tubes and ovaries.

The external genitalia should be inspected thoroughly yet gently. Any direct manipulation of the clitoris, unless it is being assessed as in cases of suspected virilization, should be avoided. In the latter case, the clitoral size should be determined by measuring the length and width of the glans. Normal values for a female between 11 and 15 are not more than 3 × 3 mm; for a girl between 15 and 19, no more than 5 × 5 mm.[2] A width of 10 mm is significant for virilization.[3] The urethral orifice should be inspected for any abnormalities. Usually it is easy to examine Bartholin's and Skenes glands because they are not normally palpable. However if the duct or gland is infected, it is easily located because it is enlarged and thickened. The duct should be milked to determine if there is a discharge, and if so it should be cultured.

The hymen and its anatomy should be examined for abnormalities, most of which have symptoms ranging from amenorrhea and pain with intercourse in the case of an imperforate hymen to dysmenorrhea as occurs with a septate or cribriform hymen. Depending upon the size of the hymenal perforation, the physician must decide whether to introduce a speculum. If a speculum is used, the patient should be asked whether she uses tampons with menstrual periods. If so, the physician should emphasize that the diameter of a pediatric speculum is no larger than a tampon. The speculum should be thin bladed (small Pederson) and lubricated either with a jelly or warm water, the latter being preferable because water does not affect the evaluation of a Pap smear or assessment of vaginal discharge. The speculum should first be placed on the inner thigh, and the patient asked whether it is warm enough. This allays anxiety and avoids surprising her with a cold metallic instrument on the perineum. As the speculum is inserted the physician should spread the labia and be certain that no pubic hair is in the instrument's path. The speculum is then introduced through the introitus after it is rotated in a 45° angle. The movement of this instrument should be downward, while at the same time rotating it back to a horizontal position, with the posterior blade pressed against the perineal body. This allows sufficient visualization of the cervix. The anterior blade should not be pressed upward because it causes trauma to the urethra.

The cervix should then be inspected for any abnormalities. A vaginal septum or cervical hood should alert the physician to the possibility of diethylstilbestrol (DES) exposure. An erythematous area around the cervical os, usually referred to as congenital eversion of the mucosa, is normal. This is the result of an endocervical columnar epithelium in the exocervical area.

After inspecting the walls of the vagina and the cervix, a cotton swab should be inserted into the endocervix and kept there while it is gently rotated for about 30 seconds. The swab is then streaked on a modified Thayer-Martin culture plate for *Neisseria* gonorrhea culturing. If there is a vaginal discharge, a second swab should be used to sample any abnormally large amounts of vaginal secretions. It is then placed in a separate test tube with 2 cc normal

saline or potassium hydroxide (KOH). Microscopic examination of this diluted exudate should be done on a slide with a cover slip. A Pap smear is then obtained with sampling from the endocervical canal using both a cotton swab and an Ayer's spatula. In addition, a sampling of the posterior vaginal fornix secretions should be obtained for the Pap smear.

In the pediatric patient, proper visualization of the vagina and cervix frequently can be had by inserting an otoscope through the introitus. This provides adequate visualization and is less painful than the speculum.

The bimanual portion of the pelvic exam is done last. With one well-lubricated finger inserted into the vagina and the slightly curved fingers of the other hand lightly on the abdomen, the pelvic organs are gently and quickly palpated. The cervix usually is felt first, its shape, consistency, and contour noted. An important sign that alerts the physician to a possible infection is pain upon manipulation of the cervix. If there is bleeding after the examination, this may be an indication of either a vaginocervical infection or malignancy.

The size, shape, consistency, and position of the uterine fundus are determined next. This is done by ballottement of the cervix with the intravaginal finger and concomitant light pressure applied suprapubically on the abdomen with the other hand.

The adnexa usually are felt only if they are abnormally enlarged. They are palpated by moving the intravaginal finger to one vaginal fornix, while at the same time the other hand presses gently but firmly downward on the same side of the pelvis. The same technique is repeated on the other side. Then the lateral walls and bony structures of the pelvis are evaluated. If there are any masses, they should be noted.

In the very young child, a well-lubricated finger—usually the little finger—is inserted into the rectum and the genital tract assessed.

Postexamination Discussion

After the examination, the patient and health care provider discuss the chief complaint and associated findings. This may necessitate use of visual aids. Emphasis is placed on the confidentiality that exists in a doctor-patient relationship. An adolescent should have the option of letting her parent(s) be present during the conference. All questions are answered in a direct, simple manner. Any fears or any misconceptions the adolescent may have about her sexuality are allayed and clarified. Questions posed by the parent(s) are answered, preferably with the active participation of the adolescent. This allows the patient to feel she is in control with her treatment. This is one of the most important goals of the initial gynecologic encounter.

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The Child with Ambiguous Genitalia 5

Richard H. Reindollar and Paul G. McDonough

Genital ambiguity in the newborn is a true medical emergency. Life-threatening crises may occur if a correct diagnosis is not made. The emotional well-being of the family and the long-term psychosocial development of the infant are at stake. The medical, psychologic, and social implications surrounding the delivery of the infant with genital ambiguity make expert advice imperative for the ongoing care of the child and family.

Normal sexual differentiation requires an orderly and intricate development of the gonads, internal ductal system, and external genitalia. Such development depends upon a multitude of events that begin as early as gametogenesis and the first division of the newly fertilized ova.

Ambiguity of the external genitalia may present as overt, incomplete masculinization of the male or overt virilization of the female. It also may present with only minimal anatomic alterations of the external genitalia such as hypospadias and/or unilateral cryptorchidism in the male and mild clitoromegaly in the female. Either overt or minimal external genital abnormalities must be considered forms of ambiguity, implying associated abnormalities of sexual differentiation that may originate in an abnormal germ cell chromosomal complement, faulty expression of genetic gonadal determinants, abnormal gonadal morphogenesis, or fetal adrenal endocrine malfunction. In contradistinction, the normal male and female phenotypes do not rule out similar but hidden abnormalities of sexual differentiation that may become evident during later childhood or puberty.

Normal Sexual Differentiation

Sexual differentiation begins during gametogenesis. It requires normal meiotic activity in both preconceptional oocytes and spermatogonia so that each gamete is endowed with only one sex chromosome. Sexual differentiation requires normal fertilization, and especially important is early mitotic activity of the zygote. Normal mitotic activity assures that all early embryonic cells, including the germ cells, have a normal chromosomal complement. Germ cells begin as a limited number of large well-defined cells in the endoderm of the yolk sac. Ameboid movement propels them to the hindgut and on to the genital ridge. Mitotic activity of oogonia appears to be influenced by a rise of FSH and LH in the 46XX embryo.[1] This is important in ensuring an adequate total number of germ cells in the female. Replenishment never occurs in extrauterine life. In contradistinction, mitotic activity of the spermatogenia is limited during intrauterine life because replenishment begins at puberty and continues throughout the male's reproductive life.

The initiation of testicular development at approximately 4 to 6 weeks of gestation is active and dependent upon testicular determinant genes (Fig. 5-1). These important genes are located on the short arm of the Y-

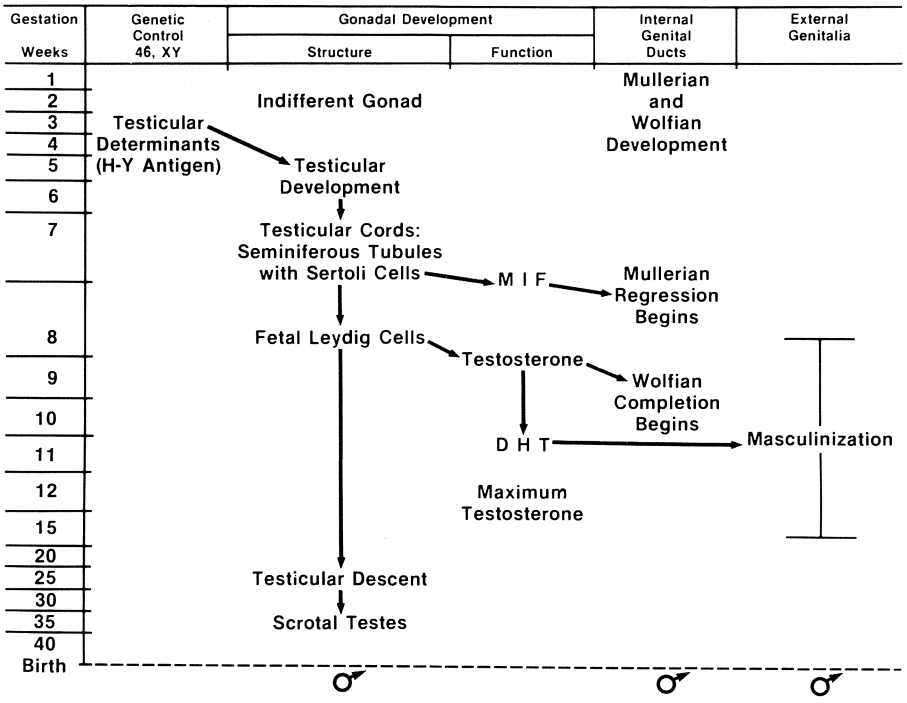

Figure 5-1. Schematic timetable of events for in utero normal male sexual differentiation.

chromosome near the centromere. They appear to be either structural genes coding for H-Y antigen production or regulatory genes controlling X- or autosomal located H-Y antigen structural genes.[2-4] Animal studies suggest that H-Y antigen produced under the control of Y-located testicular determinants engages its own receptors on gonadal cells.[4] It is this receptor-mediated event that seems to initiate medullary gonadal development along testicular lines.

In contradistinction, the initiation of ovarian development at approximately 6 to 8 weeks of gestation is passive (Fig. 5-2). Ovarian determinants are not required for triggering cortical gonadal differentiation. In the absence of testicular determinant gene expression, germ cells of XX and rarely XY complements will organize as the primitive ovarian anlage.

The primitive genital ridge is a bipotential gonad, and until gonadal differentiation begins the fetus is sexually dimorphic. Once gonadal differentiation begins, the prenatal function required for completed sexual differentiation in utero and at puberty differs markedly between embryonal testis and ovary. The testis has substantial endocrine activity during development (Fig. 5-1), whereas the ovary is capable of estradiol production, but endocrine function is limited and not requisite for further sexual differentiation. Unlike the testis, the ovary demonstrates mainly exocrine function (Fig. 5-2).

Once the primitive germ cells arrive in a developing testis, minimal mitotic activity increases their number. These spermatogonia become rapidly enveloped by developing seminiferous tubules, protected by the Sertoli cells from further mitotic and meiotic activity and atresia. Endocrine activity of the testis begins with the elaboration by the Sertoli cells of a nonsteroidal hormone, müllerian-inhibiting factor (MIF). Shortly thereafter Leydig cells appear and proliferate. As human chorionic gonadotropin (HCG) peaks during the end of the first trimester, steroidogenesis begins within the Leydig cells. Experimental evidence suggests that the early developing testis is an autonomous endocrine organ. Initial androgen production may be under intrinsic control and independent of pituitary gonadotropins or hormones such as HCG.[5] Cholesterol is synthesized and subsequently converted by a

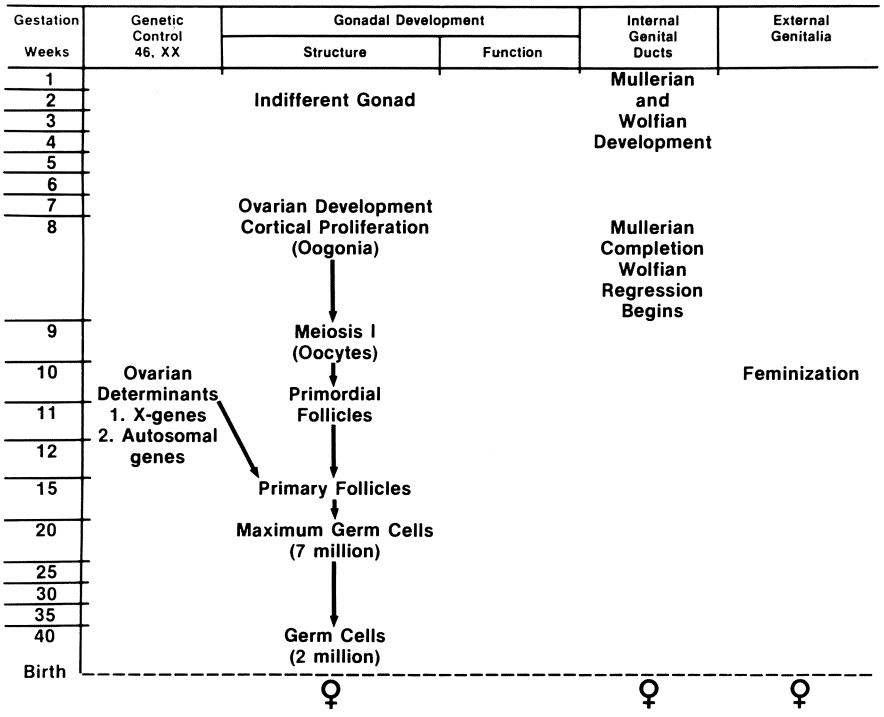

Figure 5-2. Schematic timetable of events for in utero normal female sexual differentiation.

number of enzymes to the early Δ_5 and Δ_4 androgen precursors, dehydroepiandrostenedione (DHEA)[5] and Δ_4-androstenedione. Requisite testicular endocrine function is completed with the conversion of Δ_4-androstenedione to testosterone by 17-hydroxysteroid dehydrogenase and the conversion of testosterone to dihydrotestosterone (DHT) by 5α-reductase.

Internal ductal systems accessory to the gonads and the external genitalia also are endowed at conception with a bipotential state (Figs. 5-1 and 5-2). The undifferentiated embryo develops primitive müllerian and wolfian structures in parallel. Müllerian development will progress until complete unless stopped by the MIF. In contrast, wolfian development progresses only under the direct effect of testosterone. Elaborate rabbit experiments by Jost have shown that each gonad is responsible for the development of its own accessory structures.[6] These effects of MIF and testosterone seemingly are only local and unilateral. The external genitalia passively develops along female lines unless testosterone is converted intracellularly to dihydrotestosterone. Translocation of DHT into the nucleus by its own cytosol receptors must follow for DNA activity and protein synthesis. Leydig cells steroidogenesis peaks after approximately 9 weeks of gestation. Masculinzation of the external genitalia follows with labioscrotal fusion, extension of the urethral groove onto the genital tubercle, and elongation of the genital tubercle, and usually is completed by 15 weeks of gestation. Testicular descent is controlled by a number of morphologic and endocrine factors. Androgen production and gonadotropin stimulation appear to be of prime importance; descent usually is not complete until after 32 weeks of gestation.

Unlike the testes, which function primarily as fetal endocrine organs, the early ovary has mainly exocrine activity centering around germ cell mitosis and meiosis. Under the influence of elevated gonadotropins, ovarian germ cells markedly proliferate and reach a maximum endowment of 6–7 million by 20 weeks of gestation.[1] Oogonia that enter meiosis I become oocytes. Most of the oocytes continue the early meiotic activity to the point of atresia. Only 500,000 oogonia are arrested in prophase of meiosis I after birth. It is this critical step, designed for preservation of the

follicular endowment, that requires ovarian determinant gene action. Such genes are located on both arms of both X-chromosomes and probably also on autosomes. Jirasek has shown histologically that germ cells that are preserved in prophase of meiosis I become surrounded by a mantle of follicular cells and compact stroma.[7] Germ cells destined to undergo atresia are incompletely surrounded by this mantle of primitive granulosa cells. Fetuses with Turner's karyotypes that are missing ovarian determinant genes rarely are able to give their germ cells the protection of this surrounding layer of cells. Their oocytes are incompletely surrounded, the results of which are premature follicular atresia and germ cell depletion. The ovarian determinant genes may control the development of this mantle, which then elaborates a meiosis I inhibitor. It also is possible that these genes control the elaboration of a protective substance from the granulosa cells, and that a critical amount is necessary to arrest meiosis I. A number of nonsteroidal regulators of ovarian function have been studied. Oocyte maturation inhibitor (OMI) is one such substance that appears to be produced by the granulosa cells and is essential for the suspended or arrested state of meiosis I.[8] Such germ cells remain in the immature dictyate stage of meiosis I prophase until shortly prior to ovulation. It is the lack of endocrine activity in the fetal ovary that allows for the passive development of the müllerian system and female external genitalia. Similarly, it is this excess exocrine germ cell activity that makes future reproduction possible.

Abnormalities of Sexual Differentiation

A classification of abnormalities of sexual differentiation is outlined in Table 5-1. An

Table 5-1. Two Classifications for Patients with Abnormalities of Sexual Differentiation.

Original Classification	New Classification
Male pseudohermaphroditism	I. Deletion syndromes without Y cell lines
	II. Deletion Syndromes with Y cell lines (45,X/46,XY)*
	III. 46,XY
	A. Gonadal dysgenesis (Swyer's sydrome)
	B. Empty pelvis; agonadia*
	C. Enzyme deficiencies
	1. 17-ketoreductase deficiency*
	2. 17α-hydroxylase deficiency*
	3. 5α-reductase deficiency*
	D. Testicular feminization
	1. Complete*
	2. Incomplete*
	E. Nonendocrine/non-sex chromosome defects*
	F. 46,XY true hermaphrodite*
True hermaphroditism	IV. 46,XX/46,XY true hermaphrodite*
Female pseudohermaphroditism	V. 46,XX
	A. 46,XX true hermaphrodite*
	B. 46,XX sex reversed male
	C. Congenital adrenal hyperplasia
	1. 21-hydroxylase deficiency forms*
	2. 11β-hydroxylase deficiency*
	3. 3β-ol-dehydrogenase deficiency*
	D. Maternal androgen
	1. Drug*
	2. Tumors of pregnancy*
	E. Nonendocrine/non-sex chromosome defects*
	VI. 47,XXY

*Syndromes presenting with sexual ambiguity.

older classification system uses the terms pseudohermaphrodite and hermaphrodite. A male pseudohermaphrodite has a 46,XY karyotype and external genitalia contradictory to that genetic sex. A female pseudohermaphrodite has a 46,XX karyotype and contradictory external genitalia. A true hermaphrodite has varying degrees of genital ambiguity and both ovarian follicles and testicular tissue, i.e, seminiferous tubules. A newer classification demonstrates a degree of overlap between some of these syndromes and is based purely upon the patient's karyotype. Those with abnormalities of sexual differentiation present because of deletion syndromes. These persons are missing the X-chromosomal material important for preserving ovarian follicles within the developing ovaries. Similar patients are mosaics, with these deletion cell lines in association with a 46,XY cell line. These patients have asymmetric gonadal dysgenesis. Those individuals with a 46,XY karyotype may have abnormalities of sexual differentiation that are manifested as varying degrees of undermasculinization. Abnormalities producing any one of these syndromes may occur at any of the steps for normal male sexual differentiation. Similarly, patients with a 46,XX karyotype may demonstrate degrees of overmasculinization and even a near normal male phenotype. Such abnormalities may be secondary to anomalous expression of testicular determinants, endogenous maternal overproduction of androgens, or exogenously given androgens. True hermaphrodites may have either a 46,XY karyotype, a 46,XX karyotype, or both 46,XX and 46,XY cell lines. Miscellaneous syndromes unrelated to the normal systems for sexual differentiation occur in both the 46,XY and 46,XX categories. The 47,XXY patients also are included in this classification system.

Deletion Syndromes

The first deletion syndromes described are those missing X-chromosomal material. Paternal meiotic nondisjunction of the sex chromosomes previously has been considered etiologic for Turner or quasi-Turner syndromes associated with privation of X-chromosomal material. It is evident that these abnormal karyotypes more commonly result from such postfertilization errors as mitotic nondisjunction and mitotic anaphase lag. Anaphase lag of the X- or Y-chromosome and its subsequent loss at the first cell division of the zygote may result in a single cell line with a 45,X karyotype. Sometimes it appears that the early zygote unsuccessfully attempts to develop into identical twins, and one of the sex chromosomes is either lost by anaphase lag or carried along with the other sex chromosome by nondisjunction. Mosaicism occurs as the 45,X cell line becomes associated with one or more cell lines. Such an abnormal segregation of sex chromosomes in an attempt at twinning has been triggered by a structurally abnormal Y- or X-chromosome. There is an increased prevalence of normal identical twins in the sibships of patients who have deletion syndromes, which further suggests an inherent predisposition for twinning. Identical twins concordant and discordant for these syndromes have been reported.[9] The patients reported with Turner's syndrome are classically noted to have a 45,X karyotype. More often, however, these patients demonstrate forms of mosaicism, with a 45,X cell line accompanying other cell lines such as 46,X,i(Xq) or 46,XX. It really does not matter what karyotype is present because the common denominator of these syndromes is the deletion of important X-located ovarian determinant genes. The end result of privation of this chromosomal material is early follicular depletion. Persons with Turner's syndrome generally have bilateral streak ovaries, a normal müllerian system, and external genitalia that is unquestionably female.

Asymmetric gonadal dysgenesis is included in this classification. These persons have mosaicism, with 45,X/46,XY cell lines. They may have bilateral intraabdominal streak ovaries or a unilateral intraabdominal streak gonad associated with a contralateral intraabdominal dysgenetic testis. Others may have an intraabdominal streak ovary and a contralateral descended dysgenetic testis or bilateral descended dysgenetic testes. These four possibilities for gonadal differentiation are associated with the following respective phenotypes: sexual infantile Turner phenotype at puberty, Turner phenotype with isolated clitoromegaly, ovary ambiguity, and male or near normal male phenotype.[10,11] Patients with mixed gon-

adal dysgenesis are natural experiments of Jostian principles,[6] the internal ductal system developing in accordance with the accompanying gonad.

The ovaries of those with privation of X-chromosomal material will develop not unlike those of normal females. The lack of ovarian determinant genes is associated with incomplete formation of the primitive follicular mantle around the oocytes and unarrested meiotic activity.[7] Patients with Y cell lines have early and complete follicular atresia and depletion. They remain sexually infantile unless given estrogen replacement. All other Turner patients have premature oocyte depletion, which most commonly occurs during intrauterine life or childhood. Most of these patients also are sexually infantile during adolescence. Rarely, follicular depletion occurs after spontaneous puberty, short menstrual lives, and even more rarely, following pregnancy. Privation of X-chromosomal material is associated with short stature, the variable Turner phenotype, and known cardiovascular/renal malformation. Coarctation of the aorta and horseshoe kidney sometimes occur. Patients with a Y cell line have a 15–25% chance of developing gonadal ridge tumors.[12]

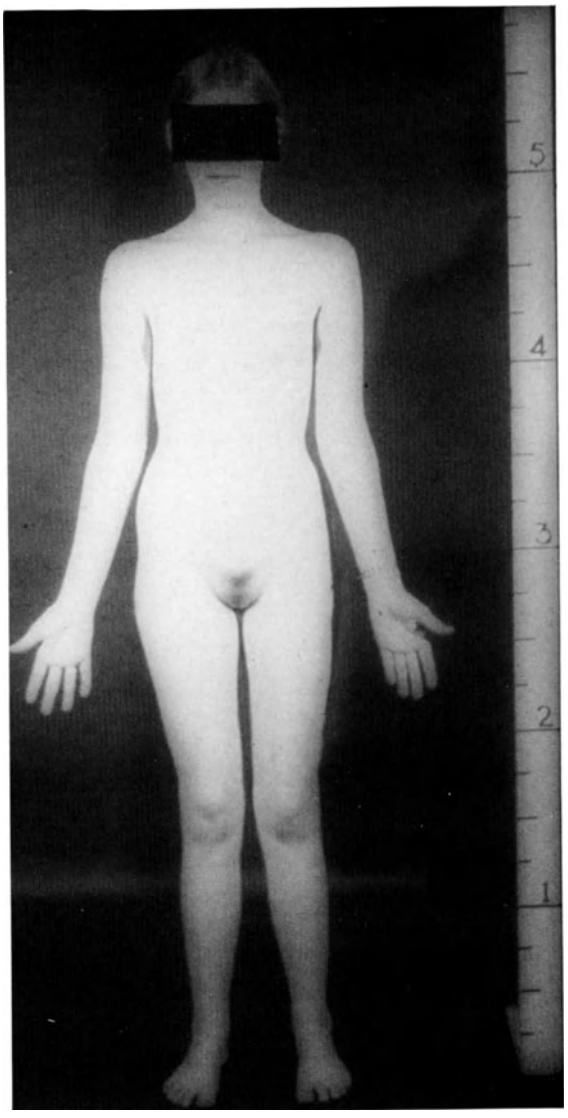

Figure 5-3. D.J., a 19-year-old girl with 46,XY gonadal dysgenesis, normal stature, sexual infantilism, and bilateral gonadoblastoma. Reproduced with permission from Tho PT, McDonough PG: Pediatr Clin North Am 28:319, 1981.

46,XY Abnormalities of Sexual Differentiation

The sexually undifferentiated fetus with a 46,XY karyotype depends upon a series of events for normal male sexual differentiation (Fig. 5-1). Abnormalities can occur at every step of this process and result in fairly predictable syndromes.

46,XY Gonadal Dysgenesis (Swyer Syndrome)

Failure of germ cell migration, teratogenic disruption of the early testis in a person capable of H-Y antigen expression, repressor gene action on the H-Y antigen locus, and abnormal gonadal receptors for H-Y antigens all have been implicated in this syndrome.[3,13] Gonads do not develop when germ cell migration does not occur. Teratogenic events may leave only primitive streak testes incapable of endocrine function. Failure of H-Y antigen production or H-Y antigen-receptor engagement may be associated with gonadal development along ovarian streak lines.[3] These patients produce neither MIF nor testosterone. They develop as normal phenotypic females with intact müllerian systems and have delayed puberty. They are at the highest risk of any patient with dysgenetic testes and Y cell lines for genital ridge tumor formation (Fig. 5-3).[11,12,14] Most cases are sporadic. A number of kindreds have been reported in which this syndrome is inherited as an X-linked recessive or male-limited dominant disorder.[13,15] Persons in these kindreds have been reported as H-Y antigen negative, an argument for the

presence of X-linked genes capable of suppressing testicular determinant genes.[3] Most persons affected in such kindreds reportedly are H-Y antigen positive, an argument for X-linked genes that code for abnormal gonadal H-Y antigen receptors.[3] Still others are H-Y antigen intermediate,[3] suggesting the deletion of a critical number of testicular-inducing genes.

46,XY Individuals with Steroid Enzyme Deficiencies

Testicular development is not a guarantee that endocrine function will be normal. Patients with enzyme deficiencies in the major steroidogenic pathways for androgen synthesis usually have varying degrees of abnormal wolfian development and/or undermasculinization of the external genitalia. These deficiencies usually are not complete but generally block production of one or more of the androgens necessary for sexual differentiation (testerone and/or dihydrotestosterone). The most common enzyme deficiencies involve 17α-hydroxylase, 17-ketoreductase, or 5α-reductase.

17α-Hydroxylase deficiency is probably the least common of the enzyme blocks.[16–19] In males, the deficiency seems to be less marked than in females. Testosterone, deoxycortisol, and cortisol generally are decreased, and hypokalemia often is present. Deoxycorticosterone (DOC) and corticosterone are secondarily increased. Renin and aldosterone may be suppressed as a result of salt retention and hypervolemia. Increased ACTH production has been considered etiologic for the exaggerated production of the zona fasciculata mineralocorticoids as well as the zona glomerulosa steroids.[17] ACTH may have an additional effect within the adrenal to impair aldosterone synthesis, possibly at the level of 18-hydroxylase (corticosterone-methyl-oxidase type I) and 18-hydroxysteroid dehydrogenase (corticosterone-methyl-oxidase type II).[19] Whereas females usually develop hypertension, males rarely have blood pressure problems because of their greater enzyme activity.[17] Despite the subnormal levels of testosterone, the wolfian systems generally are normal in 46,XY persons who have 17α-hydroxylase deficiency. There are varying degrees of undermasculinization of the external genitalia.[17] Cryptorchidism may be present. These persons usually are raised as males. The risk of tumor is probably not increased except as associated with cryptorchidism.

Persons with 17-ketoreductase deficiency (17-hydroxysteroid dehydrogenase deficiency) are relatively unable to convert androstenedione to testosterone.[20,21] Serum testosterone levels are low. The precursor compounds Δ_4-androstenedione and dehydroepiandrostenedione (DHEA) become elevated. 17-Dehydroxyprogesterone and estrone also may be elevated. H-Y antigen assays are positive in these patients suggesting that testicular development mediated by H-Y antigen is not dependent upon testosterone production.[3] The phenotypic heterogeneity that exists depends upon the degree of enzyme deficiency. The external genitalia usually are more feminine than those associated with other enzyme deficiencies, and nearly all these infants are reared as females. Testicular descent may occur (Fig. 5-4). At puberty these patients may develop hirsutism, marked clitoromegaly, and voice cracking. Breast development is not uncommon and believed to be secondary to increased serum estrone and estradiol levels. Patients with high testosterone/estradiol ratios may not develop gynecomastia.

5α-Reductase deficiency has long been considered a relative inability to convert testosterone to dihydrotestosterone in utero. The wolfian system develops normally under the

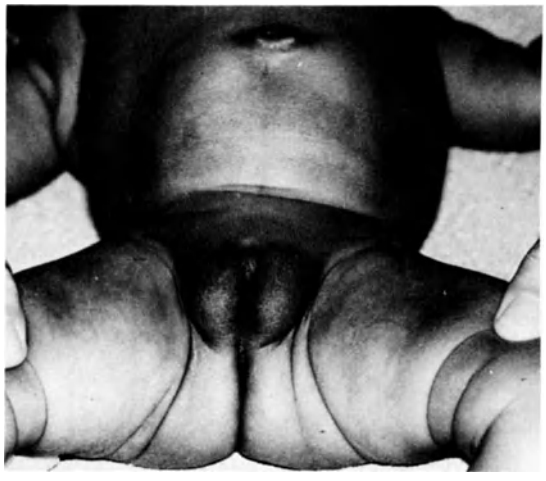

Figure 5-4. S.S., a newborn female infant with bilateral labioscrotal gonads, labioscrotal fusion, and mild clitoromegaly. Undermasculinization of this 46,XY infant was caused by 17-keto-reductase deficiency.

influence of testosterone. The external genitalia are undermasculinized but more male than female.[21] Pseudovaginal perineoscrotal hypospadias, the name often used for this syndrome, is descriptive of the phenotype. These persons have a clitoris-sized phallus, a perineal urethral orifice, and a separate blind-ending perineal pouch.[22] This blind pouch probably represents a vestige of the enlarged prostatic utricle, which usually regresses under the influence of dihydrotestosterone. Varying degrees of testicular descent occur. These persons usually are reared as males after virilization at puberty. The phallus enlarges, facial hair develops, and muscular hypertrophy and voice cracking occur.[22] It had previously been assumed that such virilization at puberty is the result of enzyme maturation during childhood, with increased production of DHT. Recent evidence suggests that testosterone and DHT share a common receptor, and that testosterone has a lower affinity for it than does DHT.[23] It is possible that testosterone produced in utero has some effect in the virilization of these males' external genitalia. Increased levels of testosterone at puberty may explain the increased masculinization at that time. It may be the effect of testosterone on the cytosol receptor rather than increased enzyme activity and production of DHT that causes the increased masculinization.[23] Tumor formation in these testes has not been described.

46,XY Empty Pelvis

A spectrum of syndromes has been described in which persons have evidence of testicular development and some degree of endocrine function but have either absent or very rudimentary testes.[24] Persons with agonadia seemingly are affected during the critical period for MIF and testosterone production. Their gonads are absent. They develop neither normal müllerian nor wolfian systems. Moreover, their external genitalia appear markedly undermasculinized. Sometimes the insult appears to occur after endocrine function has been established. Some of these patients have a small but well-formed penis, wolfian derivatives, and rudimentary testes. Others have unambiguous male external genitalia, normal wolfian derivatives, and absent testes. The latter are labeled with anorchia. Several hypotheses attempt to account for these syndromes. The insult causing agonadia and the syndrome of rudimentary testes may be an environmental agent or teratogen. Torsion and testicular arterial occlusion after masculinization of the external genitalia also might account for rudimentary testes and those with anorchia.

Androgen Insensitivity Syndrome (Testicular Feminization)[2]

Normal testicular development and endocrine function do not ensure the normal development of internal and external genitalia. Patients with androgen insensitivity syndrome are unable to convert the testosterone signal into the target organ event of masculinization because of cytosol androgen receptor defects. Genetic heterogeneity has been described with distinct variants, which produce a spectrum of syndromes for complete and incomplete androgen insensitivity.[25] The mutant genes that produce these syndromes are located on the X-chromosome, and inheritance is described as X-linked recessive.[26] A number of families have been reported to have members with these syndromes, but more than one form does not exist within a family.[25]

The phenotype of the patient with androgen insensitivity syndrome includes normal female external genitalia, a female body habitus, and normal pubertal breast development (Fig. 5-5).[26–30] Inspection of the perineum reveals a blind vaginal pouch, the vestige of an enlarged prostatic utricle. Müllerian structures are absent. Pubic hair is scanty or absent in persons with complete androgen insensitivity syndrome (CAIS). Those with the incomplete form of this syndrome (ICAIS) may have varying degrees of masculinization. Pubic and axillary hair and moderate clitoral enlargement may be present in those previously thought to have Lub's syndrome or Reifenstein's syndrome, an even more masculinized form. Recently, phenotypic males with severe oligospermia or azoospermia have been diagnosed with ICAIS, i.e., infertile male syndrome.[31,32] Testicular development for all forms is normal in utero and associated with varying degrees of descent. Seminiferous tubules are found but without evidence of spermatogenesis. The number of Leydig cells may be increased. Testicular endocrine function is

normal for both nonsteroidal hormone production (MIF) and steroidogenesis. Hormone profiles reveal normal male levels of testosterone, elevated serum LH, and normal or slightly elevated FSH levels.[27,28] Serum estrone and estradiol levels may be higher than expected for normal males, approaching female levels. It is this conversion of androgens to estrogens as well as the cellular perception of a low androgen/estrogen ratio that are responsible for such good breast development in all patients with androgen insensitivity syndrome. Testicular tumors rarely develop prior to puberty. A relatively high incidence of neoplasia, usually seminomas, has been reported for patients with the female phenotype if the testes are left in place after puberty.[29]

The initial literature generated confusion as to whether the receptors involved in this syndrome were for testosterone, DHT, or both. The prototype of testicular feminization has been described as having neither normal wolfian nor müllerian systems. This suggests that the receptor defect includes testosterone cytosol binding. Kennon et al first documented a receptor defect in this syndrome.[33] They developed a method for measuring specific DHT binding in cultured skin fibroblasts and noted a deficiency of DHT-binding protein in skin fibroblasts of some androgen-insensitive patients. Testosterone binding was not tested. A recent study of testosterone- and DHT-binding characteristics to the androgen receptor of genital skin revealed similar maximal-binding capacity (B_{max}).[23] The apparent dissociation constant (K_D) of the receptor was greater for testosterone than for DHT. This study suggests that both testosterone and DHT share a common receptor. Furthermore, DHT has greater biologic activity because it has a greater affinity for that receptor. It may be concluded that the forms of androgen insensitivity involve cytosol receptor defects common for testosterone and DHT.

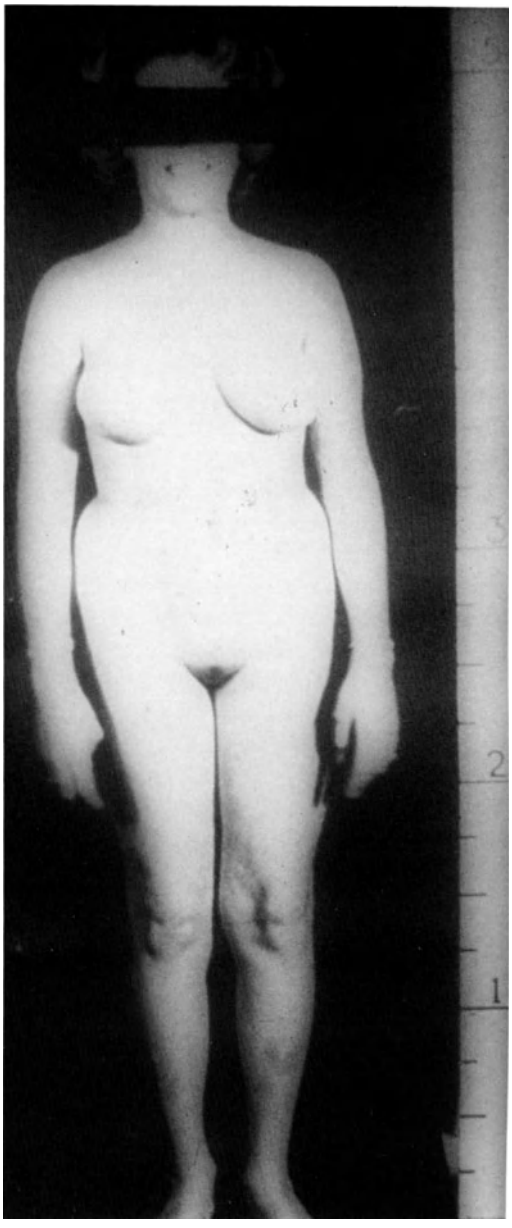

Figure 5-5. J.S., an 18-year-old patient with Tanner IV breast development, absent pubic and axillary hair, and a blind vaginal pouch. This syndrome of complete androgen insensitivity is the result of cytosol receptor deficiency for androgens.

Genetic heterogeneity described for CAIS involves two major variants,[34] androgen receptor negative patients (CAIS, AR−) with undetectable or low DHT binding in target cells, and those with positive androgen receptor assays (CAIS, AR+). There are qualitative differences in androgen receptors between CAIS, AR+ patients and normal persons. Such aberrant receptors have demonstrated a lesser affinity for DHT, a temperature-labile steroid binding site, and molybdate-labile binding stabilization.[31,34–36] It is suggested that families with a quantitative receptor defect or in whom receptor abnormalities have not been found may represent a mixture of intracellular defects, which result in androgen insensitivity. Such defects may include subtle

qualitative defects, quantitative abnormalities, and defects in postreceptor events responsible for triggering DNA translation.[31]

Nonendocrine Genital Ambiguity

Unknown teratogens have been implicated as the cause of such isolated defects as agonadia, congenital absence of the penis, duplicate phallus, epispadias, and cloacal formation in the 46,XY infant. Autosomal anomalies also have been associated with numerous somatic abnormalities, including the external genitalia. The D/G chromosome groups most commonly are involved. In particular, deletion of the long arm of chromosome 13, e.g., 46,XY,del(13)(q) produces the most consistent external genital abnormalities (Fig. 5-6).

True Hermaphroditism

Individuals who have both ovarian and testicular tissue fit the definition for true hermaphroditism. Ovarian follicles and semniferous tubules must be present. The karyotypes of such patients are characteristically 46,XY, 46,XX/46,XY, or 46,XX (Table 5-1).[37-39] Occasionally, true hermaphrodites have forms of mosaicism such as 45,X/46,XY.[38] Most frequently, however, those with true hermaphroditism have a 46,XX karyotype.[37-39]

Concomitant ovarian and testicular development may occur within the same gonad, producing an ovotestis, i.e., unilateral or bilateral gonadal hermaphroditism.[39] While there is often a sharp demarcation between the ovarian and testicular components, occasionally the testicular tissue is embedded in the medullary portion of the gonad surrounded by ovary.[37-39] Alternating gonadal hermaphroditism also occurs with an ovary on one side and a contralateral testis. In a review of 806 gonads of true hermaphrodites, 108 (22%) were testes. The location was scrotal in 63%, inguinal in 14%, within the internal inguinal ring in 1%, and abdominal in 22%.[39] The ovarian tissue in the gonads of true hermaphrodites is typically better preserved histologically, endocrinologically, and exocrinologically than is the testicular component. Internal ductal systems are dependent upon the associ-

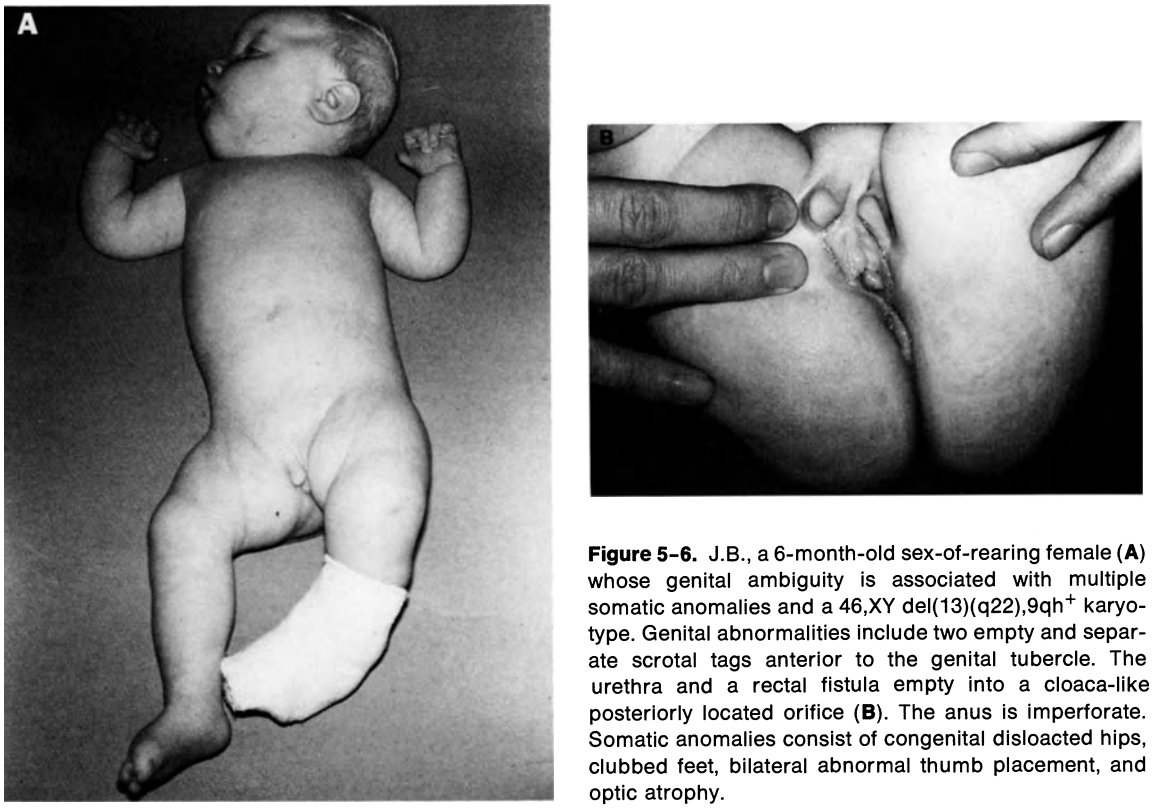

Figure 5-6. J.B., a 6-month-old sex-of-rearing female (**A**) whose genital ambiguity is associated with multiple somatic anomalies and a 46,XY del(13)(q22),9qh$^+$ karyotype. Genital abnormalities include two empty and separate scrotal tags anterior to the genital tubercle. The urethra and a rectal fistula empty into a cloaca-like posteriorly located orifice (**B**). The anus is imperforate. Somatic anomalies consist of congenital disloacted hips, clubbed feet, bilateral abnormal thumb placement, and optic atrophy.

ated gonad and its degree of differentiation.[39]

Most true hermaphrodites have at least a unilateral müllerian system accompanying an ovary or an ovotestis that, if left intact, will function at puberty. The wolfian system may accompany the testis or ovotestis and occasionally is on the same side as the müllerian system. The development of müllerian and wolfian derivatives on the side of an ovotestis depend upon the amount of MIF and testosterone produced. The external genitalia are ambiguous and usually extremely undermasculinized because of suboptimal testosterone production. Labioscrotal fusion may occur and form a urogenital sinus into which the urethra and vagina empty. More often the vagina empties into the distal urethra. Genital tubercle enlargement is suboptimal in development and associated with severe hypospadias and more often a perineal urethral orifice. These infants have historically been reared as males because the masculinization, although usually poor, is often associated with a descended gonad (Fig. 5-7).[37,39] Pubertal masculinization secondary to endogenously produced androgens or exogeneously given testosterones is poor and often results in gender identity problems. True hermaphrodites diagnosed after puberty demonstrate more feminization than virilization. Breast development[37,38] and cyclic menstruation are common. This is further evidence that ovarian endocrine function is better than that of the testes. Whereas only a few normal germ cells are identified in the testicular component, numerous primordial follicles usually are present. The ovarian exocrine activity often is associated with normal gametogenesis. At least six true hermaphrodites have been reported in the world literature as having become pregnant.[40]

Although the etiology for true hermaphroditism is unclear, there are several hypotheses. Patients with 46,XX/46,XY and 46,XY karyotypes usually have alternating gonadal hermaphroditism, i.e., an ovary on one side and a contralateral testis.[39] It is believed that they represent whole body chimerism, with longitudinal fusion of 46,XX and 46,XY embryos.[41] Under this hypothesis, the 46,XY true hermaphrodites have an undetected 46,XX cell line. Occasionally, persons with 46,XY karyotypes in peripheral blood have shown 46,XX cell lines in ovarian tissue.[37] Patients with 46,XX karyotypes most often have unilateral or bilateral gonadal hermaphroditism, i.e., ovotestes.[39] True hermaphrodites usually are H-Y antigen positive or intermediate.[3] This suggests that testicular determinants for the

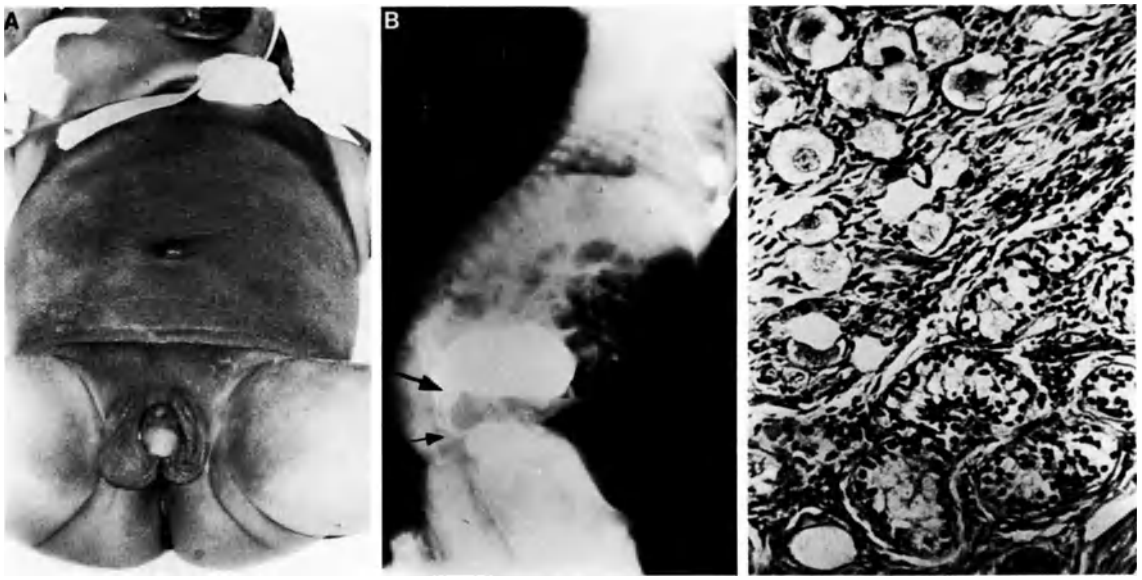

Figure 5-7. D.P., a sex-of-rearing female true hermaphrodite (**A**) with a 46,XX karyotype and a right labioscrotal ovotestis (**C**). Genitography (**B**) demonstrates a small vagina (*small arrow*) which empties into the larger distal urethra (*large arrow*).

46,XX person are translocated onto the X-chromosome or an autosome. Anomalous inheritance of Xg blood groups in several families suggests H-Y interchange.[3,41] The intermediate levels of H-Y antigen in the tissues of some patients have led to the theory that reduced H-Y antigen production might be associated with ovotestis formation.[3,41] Several familial aggregates of 46,XX true hermaphrodites suggest that a mutant autosomal gene, most likely dominant, may be etiologic.[41] It also has been proposed that partial expression of such a gene might produce the 46,XX sex-reversed male.[41] Finally, the 45,X/46,XY mosaic true hermaphrodites are not as well understood. By definition, many fetuses with asymmetric gonadal dysgenesis are true hermaphrodites. During midgestation they may have a developing ovary with multiple follicles undergoing unabated meiotic activity and a contralateral developing testis. At birth, true hermaphroditism is no longer present because of ovarian follicular depletion and streak formation. Conceivably, the rare 45,X/46,XY fetus might have preserved a few follicles in the streak ovary and, therefore, be classified a true hermaphrodite. These persons may otherwise be no different than the majority of persons with mixed gonadal dysgenesis.

46,XX Abnormalities of Sexual Differentiation

The development of the 46,XX bipotential embryo is passive. Unless testicular determinants are expressed, cortical gonadal development occurs; unless MIF and androgens are elaborated, the müllerian system develops until it is complete; and without androgens, the external genitalia will feminize. Whereas abnormalities of sexual differentiation in the 46,XY fetus require errors of deletion or interruption, similar defects in the 46,XX fetus require addition errors. As has previously been discussed, the 46,XX true hermaphrodite probably has translocation of testicular determinants onto the X-chromosome or an autosome. Normal female differentiation is interrupted by the additional expression of these testicular determinants. The 46,XX abnormalities of sexual differentiation are influenced by either the anomalous expression of testicular determinants or by androgens. The 46,XX true hermaphrodite is discussed above.

46,XX Sex-Reversed Male

Normal male phenotypic sexual differentiation requires testicular determinant expression. This typically has been associated with a 46,XY karyotype. At least 135 phenotypic males with a 46,XX karyotype have been described in the literature.[42] These men resemble the Klinefelter phenotype in a number of ways, including masculine appearance, small but well-differentiated penis and scrotum, and descended testes with abnormal histology and azoospermia. Androgens may be normal or low, and gonadotropin excretion is normal. Unlike the Klinefelter patients, these men may be shorter than normal XY males. Furthermore, tooth size is smaller and similar to that of females.[42] Less than 10% have hypospadias. Most of these men are infertile, with small testes or abnormal secondary sexual development. The etiology for this anomalous expression of testicular determinants in a 46,XX individual is speculative. Mosaicism has been considered, but evidence is not convincing. Mendelian gene mutation, translocation, X-Y interchange, minimal deletions, or preferential inactivation of an X-chromosome are all possibilities.[42]

Congenital Adrenal Hyperplasia

The most common abnormality of sexual differentiation includes disorders of adrenal steroidogenesis produced by enzymatic deficiencies (Fig. 5-8). The estimated incidence of congenital adrenal hyperplasia (CAH) in Europe and the United States is between one in 5000 and one in 15,000, respectively, with the greatest incidence found in Alaskan Yupik Eskimos.[43] Gene frequency may be second only to that of cystic fibrosis. CAH should be suspected in all babies with genital ambiguity because of its frequency and, more importantly, because it can be life threatening to the newborn.

The most frequent enzyme deficiency is 21-hydroxylase.[43–45] Reports of CAH also have included deficiency of 11β-hydroxylase, hydroxysteroid dehydrogenase, 17α-hydroxylase, and cholesterol desmolase. Genital ambiguity most frequently is found in the 46,XX fetus who has 21-hydroxylase and 11β-hy-

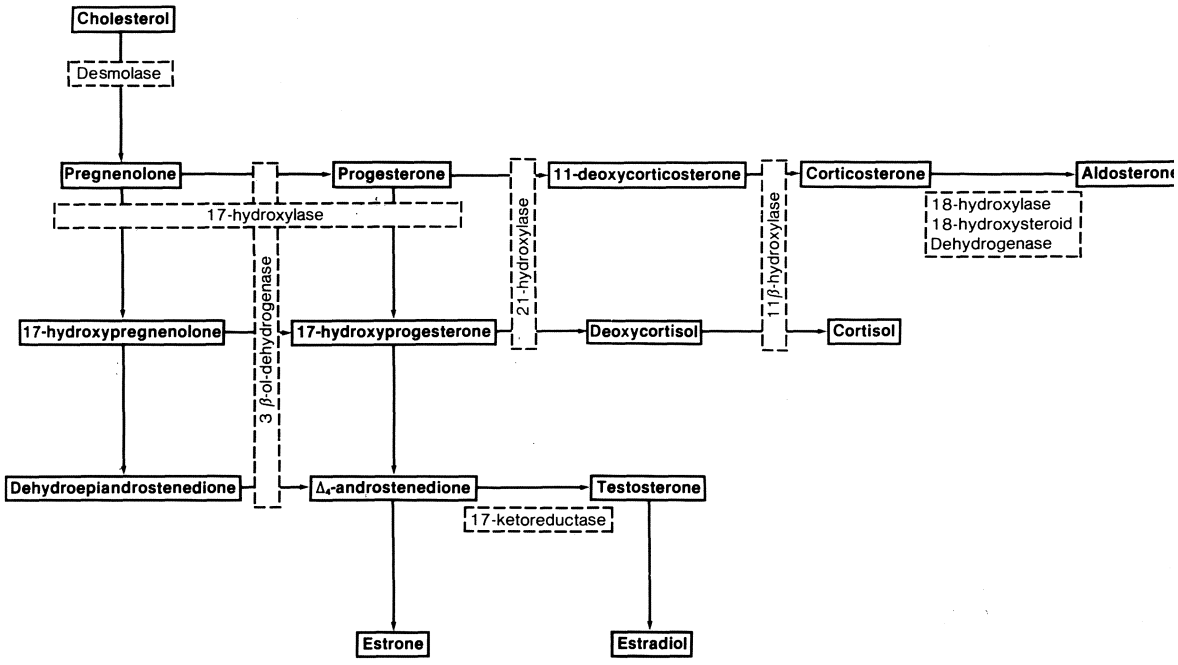

Figure 5-8. Schematic representation of the major steroidogenic pathways. Common enzyme deficiencies include 21-hydroxylase and 11β-hydroxylase deficiencies. Less frequently, deficiencies for 18-hydroxylase, 18-hydroxysteroid dehydrogenase, 17-hydroxylase, 3β-ol-dehydrogenase, cholesterol desmolase, and 17-ketoreductase occur.

droxylase deficiencies. Subnormal levels of cortisol stimulate ACTH release with further adrenal steroid stimulation and the accumulation of androgens.[43] The fetal adrenal begins to function during the third month of development. By the time adrenal androgens are significantly elevated, the ovaries are undergoing normal exocrine activity, the wolfian system already has regressed, and the müllerian system is completing development. The high adrenal androgen level may influence only the development of the external genitalia. Labioscrotal fusion begins posteriorly to anteriorly, covering over the vaginal vestible and forming a urogenital sinus (Fig. 5-9).[46] More marked androgen overproduction may cause varying degrees of clitoral hypertrophy and occasionally displacement of the urethral orifice onto the genital tubercle. The extent of virilization of the 46,XX fetus varies, even within the same family. There may be a spectrum of anatomic changes that range from minimal clitoromegaly and mild labioscrotal fusion to varying degrees of hypospadias. In the extreme, the female may have a normal penile urethra and lack only scrotal

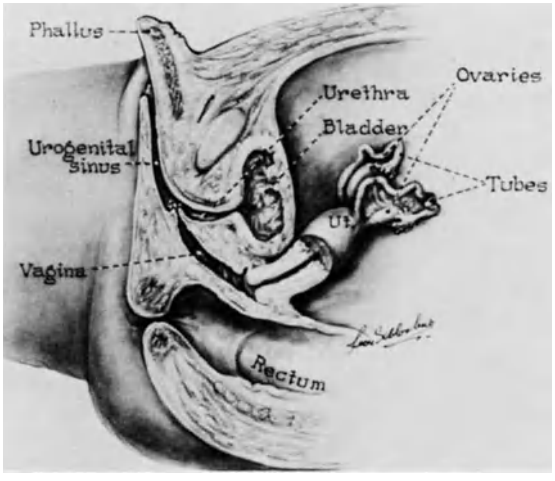

Figure 5-9. Schematic drawing of the relationship between urethra and vagina in patients with congenital adrenal hyperplasia. Typically, labioscrotal fusion occurs posteriorly to anteriorly forming a urogenital sinus. Varying degrees of clitoromegaly occur with occasional placement of the urethra onto the genital tubercle. Reprinted with permission from Jones HW Jr, Scott WW: In Jones HW, Scott WW (eds): Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. Baltimore, Williams & Wilkins, 1971, p 338.

gonads. It should be remembered that the 46,XX infant with one or two gonads in their respective labioscrotal pouches does not have CAH. Normal ovaries may herniate but do not descend further than the inguinal ligament. Infants left untreated will continue to masculinize. Excess androgens will accelerate childhood growth and cause early epiphyseal fusion. If properly treated, these patients are potentially fertile. Skin hyperpigmentation is commonly associated with these defects, the degree of pigmentation often reflecting the severity of the disease.

The most common enzyme deficiency associated with CAH is 21-hydroxylase.[43–45] This enzyme is necessary for the critical first step in converting progesterone to deoxycorticosterone (DOC) and 17-hydroxyprogesterone to deoxycortisol. There are two forms of this syndrome that may be responsible for abnormal genital differentiation, i.e., simple and salt-wasting. An adult onset form of 21-hydroxylase deficiency and a cryptic form also have been identified.[47–49] While the extent of virilization may differ within a given family, the form of the deficiency does not. The genes controlling these processes are located on chromosome 6 in close association with the HLA-B locus and between the loci for HLA-A and glyoxalase I.[43,50] They act as autosomal recessive genes with gene frequency of one in 100 and carrier frequency of one in 50. It was once believed that the difference between the two forms was quantitative, the salt-wasting form resulting from a more severe enzyme deficiency. An alternate hypothesis suggests possible autonomy between zona glomerulosa and zona fasciculata.[43] Negligible 17-hydroxylase activity occurs in the outer zona glomerulosa. It is here that progesterone is converted to aldosterone step by step. Control for aldosterone formation in the zona glomerulosa appears to be primarily through the renin-angiotensin system and by the serum potassium concentration. Only indirectly does ACTH affect the zona glomerulosa. The inner zona fasciculata layer has 17-hydroxylase activity and under the stimulation of ACTH converts 17-hydroxyprogesterone to cortisol. The zona fasciculata also may produce the aldosterone precursors from progesterone but lacks the enzyme necessary for the terminal step of aldosterone synthesis.

The new hypothesis suggests that only the zona fasciculata is affected in the simple 21-hydroxylase deficiency. In salt wasting, it appears that the defect also is present in the zona glomerulosa. Whatever mechanism is responsible for the biochemical differences between these two forms of 21-hydroxylase deficiency, it is the profound deficiency of aldosterone that produces the resultant hyponatremia, hyperkalemia, and vascular collapse in the severe form. This electrolyte imbalance may not occur until the second week of life. With increased ACTH stimulation of the zona fasciculata, androgens accumulate in both forms and virilize the external genitalia. Suppression of ACTH by glucocorticoid replacement usually will normalize androgen production. Mineralocorticoid replacement is important in maintaining normal sodium and potassium balance in this severe form. Suppression of the renin-angiotensin system in these persons will further fine tune androgen production because it appears that angiotensin II also stimulates ACTH. Some persons with the simple form also show increased renin activity.[43,51,52]

The use of mineralocorticoids in these patients also has brought about better androgen suppression. While it was once thought that 11β-hydroxylase deficiency occurred in less than 5% of all patients with CAH,[43] recent evidence suggests that this form of CAH may be underdiagnosed, and that as many as 16% of CAH patients will have 11β-hydroxylase deficiency. There are at least two types of this syndrome in which deoxycorticosterone cannot be hydroxylated to cortisol. One form affects the cortisol pathway only (17-hydroxylated steroids), whereas the other appears to affect both the 17-hydroxy and 17-deoxy pathways. Both forms can cause severe or partial defects.[45] It is believed that in some persons the defect occurs in both zona glomerulosa and fasciculata. Evidence is mounting to suggest that the decreased 11β-hydroxylase activity is limited to the zona fasciculata in those with CAH.[43] Recent studies also suggest a concomitant defect of 18-hydroxylation in patients with 11-hydroxylase deficiency.[43]

Hypertension has been the hallmark of the syndrome with 11β-hydroxylase deficiency. It previously was thought to be secondary to excessive DOC production and its mineralo-

corticoid effect.[43,45] Hypertension may not occur in the majority of persons with this syndrome, and then only in later years. A large series now refutes the idea that hypertension is caused by DOC.[45] Those with adequate suppression of DOC may have persistent hypertension; also, DOC infused into animals does not cause hypertension. Those with mild defects and only moderate elevations of DOC are sometimes hypertensive, whereas others with high DOC values and severe defects may be normotensive. The suggested association of 18-hydroxylase deficiency with this syndrome has led some investigators to speculate that hypertension may be caused by a DOC metabolite with more marked mineralocorticoid action (18-hydroxydeoxycorticosterone). Reports of salt-wasting in a few patients with 11β-hydroxylase deficiency[45] have added further confusion to the biochemical aspects of this syndrome.

The diagnosis of CAH is made in the newborn with genital ambiguity and undescended testes by demonstrating elevated levels of 17-hydroxyprogesterone and the androgens Δ_4-androstenedione, testosterone, and dehydroepiandrostenedione-sulfate.[53] Cortisol levels may be depressed. The measurement of 11-deoxycortisol and DOC may help to differentiate 11β-hydroxylase deificency from 21-hydroxylase deficiency.[43] These immediate precursors to cortisol and corticosterone are elevated in 11β-hydroxylase deficiency. Renin activity may be elevated in 21-hydroxylase deficiency and suppressed in 11β-hydroxylase activity. Moreover, ACTH stimulation studies may make the specific enzyme deficiency more evident, with a significant increase in the precursor-to-product ratio.[53,54] Serial electrolytes will identify the infant with the salt-wasting form of 21-hydroxylase deficiency. HLA genotyping in families who have a child diagnosed with 21-hydroxylase deficiency can confirm both the homozygote and heterozygote states.[43,50] The gene for 11β-hydroxylase deficiency is autosomal recessive but not linked to the HLA loci.[44] Glucocorticoid replacement is necessary in all those with 21-hydroxylase deficiency and 11β-hydroxylase deficiency. Mineralocorticoid replacement is necessary for patients with salt-wasting 21-hydroxylase deficiency; it possibly provides better androgen control for those with simple blocks for 21-hydroxylase, but who also have increased renin activity.[43] These patients outgrow their need for the mineralocorticoid as they produce such natriuretic hormones as progesterone. Blood levels of 17-hydroxyprogesterone may provide relative information for glucocorticoid control. However, patients may be under good control and still have elevated 17-hydroxyprogesterone values. Δ_4-Androstenedione appears to be the best marker for control of androgen overproduction.[55] Serum testosterone also is helpful in all prepubertal patients and adult females.

Maternal Androgen Exposure

The placenta has the ability to aromatize androgens to estrogens and prevent masculinization of a female fetus. Under some conditions, testosterone levels may become high but usually do not affect the female fetus. Factors that may overcome this normal protective mechanism include exceedingly high androgen concentrations, exposure during the critical end of the first trimester, and alterations of the native androgen molecules, which may make aromatization difficult.[56]

The conditions most commonly associated with increased endogenous production of androgens (excluding CAH) include ovarian and occasionally adrenal neoplasms.[56,57] On rare occasions, ovarian tumors have been associated with high androgen levels and masculinization of the female fetus. A few of these tumors such as the arrhenoblastoma and the Leydig cell tumor produce androgens. Other epithelial tumors seem to stimulate androgen production by the surrounding ovarian stroma. This phenomenon appears to be greatly enhanced during pregnancy, presumably by HCG. A few epithelial tumors, often metastatic to the ovary, have been reported during pregnancy that resulted in masculinization of the female fetus. The most common ovarian tumor that is etiologic for androgen over-production and female pseudohermaphroditism is luteoma of pregnancy.[56–58] This solid tumor appears to be HCG-dependent and usually disappears after pregnancy.[56] It may become large, is usually unilateral, and often produces very high levels of androgens. While considerable maternal virilization occurs, the female fetus most often is spared. Most cases previoulsy labeled idio-

pathic ambiguity were probably the result of luteoma of pregnancy. It is important to distinguish luteoma of pregnancy from hyperreactio luteinalis. The multiple lutein cysts associated with trophoblastic disease have been associated with androgen overproduction and maternal virilization but not with masculinization of the female fetus.

Exogenously given testosterone for conditions such as endometriosis and the inadvertent continuation of this drug during pregnancy rarely has masculinized the female fetus. Synthetic hormones are the most common culprit in teratogenesis resulting in female pseudohermaphroditism.[56,59] Ethisterone and norethindrone, a 19-nortestosterone derivative, have been most often implicated in masculinization of the female fetus.[60] The placenta does not appear to be as efficient in aromatization of these synthetic hormones as it is with the native steroids. Birth control pills given prior to the 12th week of gestation have the most masculinizing effects on the female fetus.[56] Given after 12 weeks, labioscrotal fusion does not occur, and masculinization may be limited to clitoromegaly.[56] More recently, danazol has been reported to masculinize the female fetus.[61,62] Genital ambiguity has been significant. In one reported case, a transient congenital adrenal hyperplasia-type syndrome was produced by maternal danazol ingestion.[61]

The classification of abnormalities of sexual differentiation associated with the 46,XX karyotype includes a special cateogory. A number of these infants have had multiple somatic anomalies associated with masculinization of the external genitalia.[56,60] Such anomalies include the genitourinary, gastrointestinal, and nonreproductive endocrine systems. These disorders usually are sporadic and may be caused by unknown teratogens. Several pedigrees of two affected infants associated with consanguinity suggest an occasional autosomal recessive etiology. Finally, some infants have been labeled as having idiopathic genital ambiguity (Fig. 5-10). These infants are normal except for varying degrees of virilization of the external genitalia. The virilization, however, does not continue and normal endocrine function occurs at puberty. It is very likely that the mothers of these infants had luteoma of pregnancy.

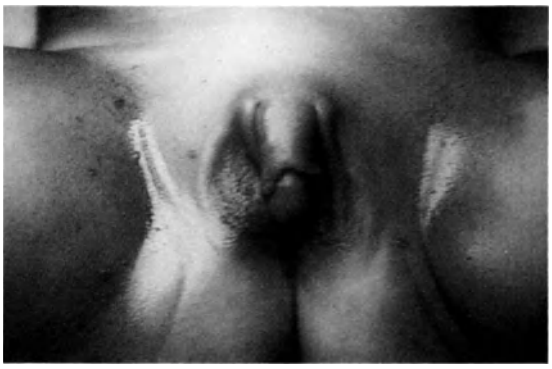

Figure 5-10. Marked clitoromegaly in an 18-month-old female infant. Evaluation revealed a 46,XX karyotype, normal endocrine profile for age, and normal internal female genitalia. The patient was labeled with idiopathic ambiguity.

Klinefelter's Syndrome

The last category of abnormalities of sexual differentiation are persons with classically a 47,XXY karyotype. Klinefelter's syndrome applies to those with other karyotypes who also have at least one Y-chromosome and two X-chromosomes. The phenotype includes small testes assoicated with azoospermia, normal male external genitalia, suboptimal masculinization at puberty, and development of gynecomastia.[63,64] Patients with Klinefelter's syndrome tend to develop a eunuchoid body habitus. These persons often have a higher prevalence of poor intellectual performance and social maladjustment than the general population. The atrophic testes histologically demonstrate hyalinization of the seminiferous tubules, absence of spermatogenesis, and Leydig cell hyperplasia. These findings are noted in the postpubertal gonad. Prior to that time, the testes appear histologically more normal and may have primary spermatogonia within the seminiferous tubules. Testosterone production is subnormal and may be half that of normal male levels. Abnormal testicular endocrine function also may be evident by elevated gonadotropins.

The etiology for Klinefelter's syndrome appears to be diverse. Both maternal and paternal nondisjunction during gametogenesis have been documented by Xg blood typing.[64] These abnormal karyotypes result from parental structural rearrangement of the

chromosomes. Postfertilization errors of mitosis have produced both mosaic Klinefelter's syndrome (46,XY/47,XXY) and other Klinefelter's karyotypes.

The Importance of Early and Accurate Diagnosis

The delivery of an infant with genital ambiguity calls for an early and accurate diagnosis and appropriate long-term management. Early diagnosis is necessary to rule out life threatening processes. It is essential to determine the sex of rearing for establishment of gender identity. It will provide for the most natural secondary sexual development in the future and possibly preserve fertility. Finally, an early diagnosis gives families at risk for recurrence the opportunity for genetic counseling.

Life-threatening problems are associated with the syndromes of genital ambiguity, including metabolic disorders, malignancies, and emotional illnesses that result from gender identity crises. Immediate metabolic disturbances associated with salt-wasting in 21-hydroxylase deficiency may begin during the first several weeks of life. Infants have died before congenital adrenal hyperplasia was diagnosed. Others have died after insufficient glucocorticoid treatment during a childhood illness. Patients with dysgenetic gonads and a Y-chromosome are at increased risk for a gonadal tumor. Gonadoblastomas and germ cell tumors such as dysgerminomas are found more frequently in gonadal dysgenesis patients. Seminomas have been discovered in patients with testicular feminization and true hermaphroditism. Continuing gonadotropin stimulation of Y-bearing germ cells, which seemingly divide more rapidly than X germ cells, provides a potential explanation for the phenomenon of tumor formation. The increased temperatures associated with the intraabdominal location of some of these testes also have been implicated in tumor formation. As a rule, the more normal the gonad and the greater its tendency for descent, the less the risk of developing a tumor. Those with 46,XY gonadal dysgenesis are at the highest risk for tumor formation, a 20–30% risk.[12] Those with 45,X/46,XY gonadal dysgenesis have a 15–20% risk.[12] Persons with testicular feminization have been reported to reach risk figures of 20% after age 30 if the testes remain in situ;[29] however, it is believed that the actual tumor risk in these testes is much less and perhaps similar to the risk for cryptorchid testes. Although there is some gonadal tumor risk for persons with gonadal dysgenesis prior to puberty, this risk for the patient with testicular feminization does not exceed 2–5% until after puberty. Tumors have been reported in true hermaphrodites but may not occur more frequently than in the otherwise normal cryptorchid male. Nongonadal malignancies also may occur more frequently in some patients with abnormalities of sexual differentiation. CAH has been associated with adrenal cortical malignancies and adrenal rest testicular tumors seeminlgy secondary to ACTH stimulation.[65,66] Other tumors of nonadrenal origin also have been reported in those with CAH, including pulmonary liposarcoma, giant cell bone tumor, hemangioendothelioma, and perirectal malignancy.[65–67] Some investigators have questioned the relationship between the genetic linkage of 21-hydroxylase deficiency and HLA antigens as etiologic for these tumors.[67] Patients with Klinefelter's syndrome develop breast malignancy 20 times more often than do normal males.[68] Life-threatening crises for individuals with abnormalities of sexual differentiation also include the adverse psychologic sequelae that may arise. A gender identity crisis, more commonly in the earlier years of medicine, has resulted in suicide for some persons afflicted with genital ambiguity at birth and subsequently inadequately diagnosed, treated, and/or counseled.

Early evaluation and diagnosis also allows for prompt assignment of sex of rearing. Prior to the era of cytogenetics, some notable physicians felt it necessary to base sex of rearing on gonadal morphology.[46] Thus, sometimes sex of rearing was changed after the neonatal period and occasionally during adolescence and adulthood. Not surprisingly, adverse emotional sequelae were common. In 1955, Money et al published a series of psychologic studies of patients with intersex disorders,[69] which stated that adverse psychologic sequelae may occur if sex of rearing is changed after the neonatal period. They further noted that the

gender identity of these patients was consistent with their sex of rearing if assigned as infants. In these infants, gender identity was independent of sex chromosomes, gonadal morphology, and genitalia at birth. Two basic tenets have developed concerning sex of rearing. First, while sex assignment can be made and apparently safely changed up to age 18 months, it should be done at birth prior to discharge from the hospital. Children past this age should not have sex of rearing changed even if an error in judgment has been made. Secondly, the single most important consideration for rearing is the future sexual function of the external genitalia. For example, true hermaphrodites historically have been reared as males. But is has now been shown that adequate pubertal sexual development usually is difficult, and that these patients fare much better if reared as females.[37]

Early diagnosis of a child with genital ambiguity will allow for long-term planning and provide for the most natural secondary sexual development. Patients at risk of developing prepubertal tumor should have early gonadal extirpation and steroid replacement shortly after age 10. Those with testicular feminization develop much better breasts from endogenous conversion of testosterone to estradiol than if given exogenous hormones. If possible, their gonads should be left in situ until after puberty. Early diagnosis also will identify those patients who may be fertile. If treated early, the fertility of CAH patients is preserved. Occasionally, true hermaphrodites may have enough follicles for pubertal development, ovulation, and rarely even pregnancy.[40] It may be possible to more frequently preserve ovarian tissue in these patients with the use of the operative microscope and frozen-section tissue studies during surgery.

Genetic counseling is extremely important for the family who has a child with an abnormality of sexual differentiation. Early diagnosis will allow many families to be reassured that a recurrence is unlikely, and it will identify those conditions that may have a genetic basis and increased risk for recurrence. Most enzyme deficiencies are controlled by autosomal recessive genes and have a 25% risk of recurrence in subsequent pregnancies. CAH is the most common of these disorders. Prenatal diagnosis is possible by measuring amniotic fluid levels of 17-hydroxyprogesterone.[70] 2-Hydroxylase deficiency also has been successfully diagnosed by HLA studies of fetal fibroblasts as compared to HLA studies of affected and nonaffected members of the same family.[71] Attempts at early prenatal diganosis and in utero treatment have been made for CAH.[72] Enzyme abnormalities such as 17-hydroxylase deficiency, 17-hydroxysteroid dehydrogenase deficiency (17-ketosteroid reductase deficiency), and 5α-reductase deficiency also are autosomal recessive. Testicular feminization syndrome and 46,XY gonadal dysgenesis in a number of persons may be X-linked recessive. Risk for recurrence in those families with an X-linked recessive disorder is 25% of subsequent pregnancies and one-third of all phenotypic females born. Similarly, one-third of phenotypic females at birth may be carriers of this disorder.

Identification, Evaluation, and Treatment

The birth of a child with genital ambiguity calls upon the immediate good judgment of the obstetrician. When the sex of an infant is in question, it is best to explain that sexual development is incomplete, and that after a few studies it will be easy to determine whether the baby is a boy or girl. Spot guesses often result in a change of sex of rearing. This should be avoided at all cost because it leaves open the nagging question of whether the final decision was correct. Gender identity and the eventual emotional well-being of the child are largely dependent upon the comments made during the first crucial moments of life.

Evaluation should begin in the delivery room. A review of the maternal history might include questions regarding maternal androgen ingestion, (e.g., oral contraceptives or danazol), and signs or symptoms related to maternal androgen overproduction, such as acne or hirsutism during pregnancy. Answers may reveal similarly affected infants or relatives. Prior neonatal deaths might provide a clue for the diagnosis of CAH. The mother's blood should be drawn in the delivery room and tested for testosterone and DHEA-S to uncover the possible luteoma, ovarian neo-

plasm, or adrenal tumor. Similar studies on cord blood may be helpful.

The infant should be given a general physical examination. Identification of Turner's stigmata or of findings such as areolar/scrotal hyperpigmentation of CAH might provide clues for diagnosis. Signs of chimerism—rarely seen in the true hermaphrodite—might include heterochromia of the iris and skin mottling.

Genital evaluation must be thorough. The genital tubercle should be placed on stretch and measured in length and width. A penis generally has a midline frenulum, whereas a normal clitoris has two lateral folds. Careful palpation for gonads is essential to determine whether they are intraabdominal, within the inguinal canals, or within the labioscrotal fold. When possible, inguinal herniation of accessory gonadal structures should be differentiated from descent of a gonad with a testicular element. Attempts should be made to determine whether there is a müllerian system and, if so, its relationship to the lower urinary system. Rectal examination might identify midline müllerian elements hypertrophied from the maternal estrogen production of pregnancy. Perineal orifices can be probed with infant feeding tubes. Once urine is obtained, the location of this orifice should be identified as the urethra. If no other orifices are identified, a second feeding tube can be inserted into the same opening and directed posteriorly to the first feeding tube in an attempt to identify a vagina. Identification of a second canal and the finding of mucus might reveal a vagina. Evaluation of this genitourinary system can be completed with genitography during the first few days of life using urethroscopy and vaginoscopy at the time of surgery.

Initial laboratory studies should include a karyotype. The buccal smear continues to provide valuable information with regard to Y-chromatin when properly obtained and prepared during the neonatal period. All infants without evidence of gonadal descent must be considered to have CAH until proven otherwise. Electrolytes should be followed closely. The diagnosis can be made with serum 17-hydroxyprogesterone and cortisol values. It is important to consider other enzyme deficiencies in these children and to attempt to diagnose them. Baseline studies for Δ_4-androstenedione, testosterone, and DHT should be obtained. Subsequent administration of HCG, 500 IU intramuscularly for 5 days, and follow-up studies will provide precursor and product information about these enzyme activities. The short-term application of testosterone cream to the genital tubercle also might test the competency of cytosol androgen receptors.

Once the diagnosis is made and the initial genital evaluation is completed, sex of rearing should be determined. Some institutions use a team approach, with a committee composed of a pediatrician, reproductive endocrinologist, urologist, and psychologist. The family should be thoroughly informed about etiology, sex of rearing, corrective surgery, and possible problems. In addition, they should be counseled by the most knowledgeable person on the team concerning expectations for future sexual development, sexual performance, and fertility. The counseling should be tailored to the education and degree of sophistication of the family. While some data might be helpful in the explanation, other information can be equally detrimental. The family should not be told that a child is a true hermaphrodite. Detailed explanations can cover the information without using that term with its frightening and negative connotation. Moreover, it is essential that the physician be convincing in assigning sex of rearing to the child. The infant always must be referred to as a boy or a girl from that point on. The physician should be able to answer all of the family's questions to their satisfaction so that they too have no question about their child's sex. Occasionally it is important to tell an educated family that the karyotype of a sex-of-rearing female is 46,XY, because children today learn in school about karyotypes and the difference between 46,XX and 46,XY chromosome complements. It is best to discuss with these families the fact that sexuality depends upon a multitude of factors none of which are dependent upon the sex chromosomes. Money's studies support this conclusion.[69]

Corrective surgery of the external genitalia can be safetly done prior to the initial discharge of the baby. It is important that the family take home from the hospital a child

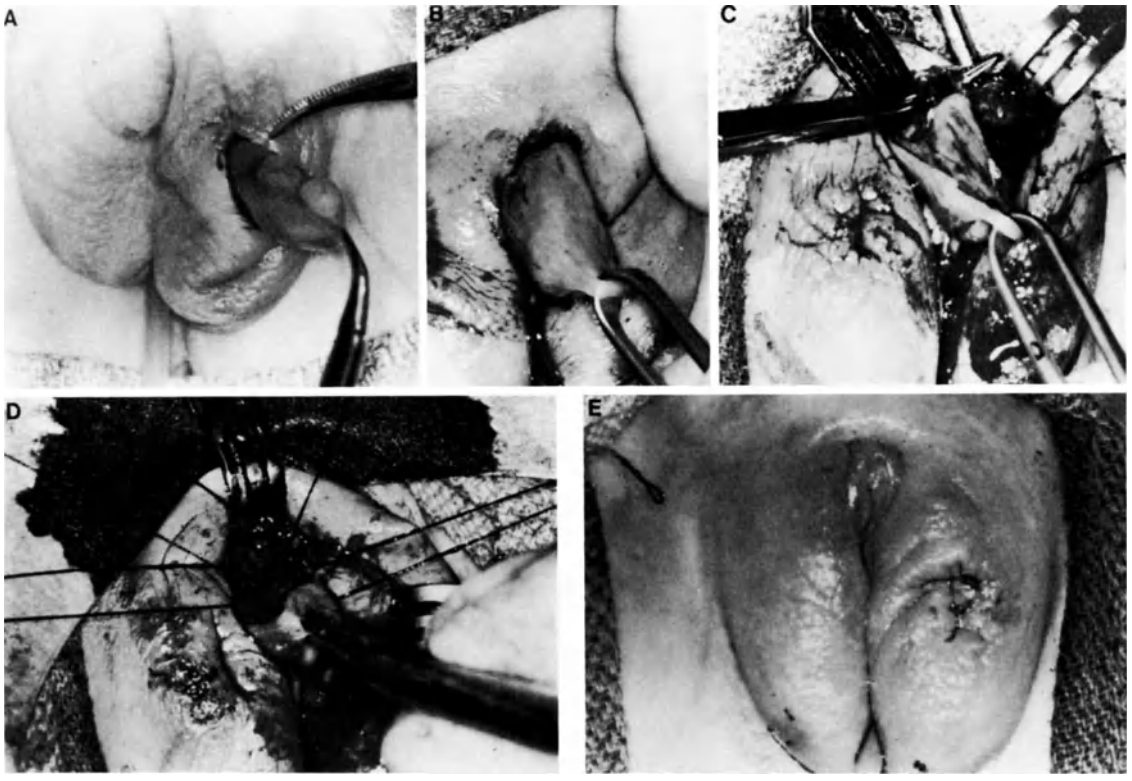

Figure 5-11. Surgery performed during the birth hospitalization might include extirpation of labioscrotal gonads (**A**) and reduction clitoroplasty (**B-E**). **B** Semicircumferential incision at the base of the genital tubercle. **C** Dissection is carried back to the symphysis where the suspensory ligament of the clitoris is transected along with proximal clitoris. The neurovascular bundle is preserved. **D** Skin over the anterior aspect of the clitoris up to the prepuce is removed and the distal tubercle is recessed onto the symphysis. **E** Immediate postsurgical result.

with external genitalia concordant with the sex of rearing. Such surgery might include extirpation of the labioscrotal gonads and/or reduction clitoroplasty (Fig. 5-11). An intra-abdominal gonad can be left in place and removed later during infancy or early childhood.

Summary

Normal male and female sexual differentiation begins with gametogenesis. Both male and female sexual differentiation follow a timetable of events with predictable development of the gonads, internal genital ducts, and the external genitalia. Completed sexual maturation occurs during puberty. Abnormalities of sexual differentiation may occur at any step along the way and may result in abnormal differentiation of the gonads, the internal genital ducts, or the external genitalia. The end results of these abnormalities produce predictable clinical syndromes. While many of these defects of sexual differentiation are evident at birth, others will not be identified until puberty when the adolescent may have aberrant external maturation or remain sexually infantile.

Genital ambiguity in a newborn represents a true medical emergency. Early and expedient diagnosis is essential to avoid life-threatening problems, to determine sex of rearing, to provide for appropriate immediate and long-term treatment, and to ensure that the family obtains adequate genetic counseling. Medical and surgical treatment should begin during the birth hospitalization, and the child should leave the hospital with its external genitalia concordant with sex of rearing. Finally, the

emotional well-being of the family unit requires appropriate education and ongoing counseling.

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Gynecologic Problems of Adolescence 6

Joseph S. Sanfilippo and Marvin A. Yussman

Abnormal vaginal bleeding is one of the most common adolescent gynecologic problems. It is a cause of anxiety both for patient and parent. This chapter presents an orderly approach to the differential diagnosis and treatment of abnormal uterine bleeding. The importance of defining an underlying endocrinologic or hematologic abnormality as well as understanding the pathophysiology of the problem is emphasized.

The amenorrheic patient also presents an interesting endocrinologic challenge to the physician. Hypothalamic-pituitary abnormalities must be correlated with alteration of ovarian function when considering the differential diagnosis of amenorrhea in the adolescent. In addition, problems of oligomenorrhea and hirsutism frequently begin at this age. Androgenic hyperactivity of the ovary and the adrenal glands must be considered when diagnosing menstrual aberrations.

Acute and chronic pelvic pain is a common gynecologic problem in teenagers. Diagnostic laparoscopy often is an integral part of the assessment of pelvic pain. Dysmenorrhea accounts for frequent absenteeism from school and work. Because early diagnosis and treatment of problems such as endometriosis is important, the authors have devoted a large part of the chapter to evaluation and management of this problem. Because physicians now have a greater understanding of the causes of dysmenorrhea and are able to offer effective therapy, the teenager no longer need fear menstruation.

Dysfunctional Uterine Bleeding

The term dysfunctional uterine bleeding has long been used to describe a large number of varied irregular uterine bleeding episodes for which no specific etiology can be found. Simply put, dysfunctional uterine bleeding is irregular, painless bleeding of endometrial origin that is excessive, prolonged, or unpatterned, and for which no local or systemic cause can be identified. Under this definition, dysfunctional uterine bleeding affects 10–15% of all gynecologic patients and accounts for 15% of gynecologic surgery. It is most common during adolescence. In an effort to be more etiologically exacting, the American College of Obstetricians and Gynecologists has suggested that it be called anovulatory uterine bleeding instead of the less explicit term dysfunctional uterine bleeding.[1] Anovulatory bleeding accounts for more than 75% of cases previously included under dysfunctional uterine bleeding. Uterine bleeding episodes secondary to blood dyscrasias, submucous leiomyomata, endometrial polyps, uterine malignancy, vaginal and cervical dysplasias and adenosis, and accidents of pregnancy are not considered dysfunctional.

The hypothalamic-hypophyseal-ovarian axis has been discussed in Chapter 2. In response to the cyclic ovarian steroids that are the end products of this axis, the endometrium undergoes a predictable sequence of changes that was delineated in 1950 by Noyes et al.[2] The major characteristic of the proliferative phase

of the endometrial cycle is growth of the endometrial glands in response to the rising estrogen secretion from the developing follicles. The glands initially are small and tubular and lined with low columnar epithelium. As the proliferative phase progresses, mitosis becomes prominent. The stroma also proliferates, and is characterized by a dense and cellular appearance. Spiral arterioles, which extend to just below the surface, supply this proliferating epithelium. This proliferation is the result of estrogen stimulation of the basal endometrium left from the previous cycle's menstrual collapse. There is dramatic growth in overall endometrial height. Following ovulation, the corpus luteum continues to produce estrogen and introduces the effect of progesterone, which initiates secretory activity within the endometrial glands. Secretory vacuoles proceed from the subnuclear to the extraluminal space. Over the next 7 days, the glands become very tortuous, ultimately achieving a picket fence appearance. Several days prior to menstruation the endometrium becomes increasingly edematous. The arterioles become tightly coiled and the stromal cells large and polyhedral. Predecidual reaction is evident around the spiral arterioles. In the absence of the human chorionic gonadotropin (HCG) stimulus of pregnancy, the withdrawal of ovarian steroids initiates arteriolar constriction, the result of which is endometrial ischemia. There is rapid polymorphonuclear infiltration into the stroma from the capillary walls, and thrombin and platelet plugs appear in the superficial vessels. Endometrial breakdown ultimately occurs, which leads to necrosis and sloughing of the endometrium. There is a natural cleavage between the basal endometrium and the more superficial and hormonally responsive spongiosum layer. It is the necrotic spongiosum that collapses and desquamates, leaving the basalis from which the next cycle's endometrium regenerates under estrogen stimulus from that cycle's developing follicles.

Exposure of the endometrium to progesterone without preliminary preparation by estrogen will not evoke a withdrawal flow when the progesterone is withdrawn. Estrogen stimulation alone, however, will produce a proliferative endometrium capable of bleeding after estrogen withdrawal or in response to desquamation of devascularized hypertrophic superficial layers of the spongiosum.

There are several patterns of irregular vaginal bleeding:

Polymenorrhea: frequent irregular bleeding at less than 18-day intervals
Oligomenorrhea: infrequent irregular bleeding at intervals of more than 45 days
Metrorrhagia: intermenstrual bleeding between regular periods
Menorrhagia: excessive uterine bleeding occurring regularly
Hypomenorrhea: decreased menstrual flow at regular intervals
Menometrorrhagia: frequent, irregular, excessive, and prolonged uterine bleeding

Jones[3] reported on abnormal bleeding in more than 500 adolescent girls followed over 5 years. Anovulatory cycling accounts for approximately 75% of irregular bleeding that is without demonstrable organic cause, whereas approximately 10% of cases are ovulatory.[4] In Jones's series 108 patients had oligomenorrhea or amenorrhea.[3] Seventy-one had irregular cycles, 23 of which were attributed to psychologic causes, four to nutritional, three to dietary, six to neurologic, and the remainder to organic problems such as hypothyroidism, diabetes, congenital heart disease, and vaginitis. Eight of the 71 (11%) patients with irregular bleeding were ovulatory; the remainder were anovulatory.

Several clinical features differentiate ovulatory from anovulatory cycles. Ovulatory cycles are more consistent in length, duration of flow, and amount of bleeding. Ovulatory cycles also are frequently associated with mittleschmerz (midcycle ovulatory pain), cyclic midcycle cervial mucous discharge, and premenstrual breast tenderness. Although dysmenorrhea does not necessarily occur with ovulatory cycles, it is notably missing in anovulatory cycles. The most common feature of anovulatory bleeding is the absence of the progesterone effect on the estrogenized endometrium. Under these circumstances, bleeding occurs when endometrial growth surpasses the vascular support on which it is dependent. When this support becomes insufficient, desquamation and bleeding result, and the cycles

usually are longer and heavier than average. With continuous low circulating levels of estrogen, endometrial growth extends over a longer period, and there is a greater interval between flows. Unpredictable, and occasionally profuse, uterine bleeding results from irregular or fluctuating levels of estrogen.

The histologic appearance of the endometrium depends upon the duration and the amount of exposure to estrogen in the absence of the secretory stimulation from progesterone. Without progesterone, the endometrium maintains its characteristic proliferative appearance, with numerous stromal and glandular mitoses and pseudostratification of the glandular epithelium. A hyperplastic pattern may develop after prolonged exposure. Cystic hyperplasia with large, dilated glands has little significance. Adenomatous hyperplasia, however, demonstrates hyperplastic glands associated with budding and an increased proportion of glands to stroma. These patients have an increased risk of developing atypical endometrial hyperplasia, which is a precursor of adenocarcinoma of the endometrium. In a study of 1000 specimens from patients diagnosed as having dysfunctional uterine bleeding, 547 had proliferative endometrium and, of the remainder, 265 had endometrial hyperplasia.[5]

Perfectly regular periods should not be expected even in girls who ovulate. Some degree of midcycle spotting occurs in 60–90% of ovulating females and frank bleeding at the time of ovulation in 20%.[6] Normal cycle length varies from 26 to 34 days.

Initial attempts at diagnosing anovulation as the cause of irregular uterine bleeding should be directed toward eliminating the possibility of organic lesions of the reproductive tract and coagulation disorders. Organic disorders that resemble simple anovulatory bleeding include intrauterine benign neoplasia; reproductive tract malignancies; bleeding with early pregnancy, such as in threatened abortion, ectopic pregnancy, and hydatidiform mole; and blood dyscrasias such as thrombocytopenic purpura, von Willebrand's disease, and platelet defects. Cervical polyps, chronic endometritis, and vaginal lesions also may cause irregular bleeding. Approximately 74% of irregular bleeding in adolescents is anovulatory. Nineteen percent are primary coagulation disorders, and approximately 7% are attributable to other pathology.

The following should be included in the differential diagnosis of adolescent irregular bleeding associated with anovulation:

1. Pregnancy complications
2. Anatomic lesions
   a. Cervical or endometrial polyps, cervicitis, leiomyomata, pelvic inflammatory disease, vaginal adenosis, and cervical changes associated with diethylstilbestrol (DES) exposure
   b. Malignancies
   c. Trauma or foreign bodies in the vagina or uterus
3. Hypothyroidism, adrenal disorders, diabetes
4. Coagulation disorders
5. Polycystic ovary syndrome
6. Miscellaneous factors affecting hypothalamic function
   a. Emotional stress
   b. Medications

Irregular bleeding in the ovulatory patient usually is the result of an anatomic abnormality. However, endocrinologic causes for irregular bleeding in an ovulatory cycle include a short proliferative phase as determined by early basal body temperature elevation and a short luteal phase.

These hormonal abnormalities usually progress to oligomenorrhea and ultimately to amenorrhea. An endometrial biopsy will determine the cycle phase and diagnosis. The long proliferative phase manifests as oligomenorrhea and infrequent ovulation and usually is associated with entities such as polycystic ovary syndrome. The mechanism is thought to be a decreased follicular response to gonadotropin, which results in abnormal FSH/LH ratios. This frequently is seen in the adolescent and is the most common cause of chronic anovulation syndrome. Corpus luteum insufficiency, which results in the short luteal phase syndrome, may have a variety of causes, including primary ovarian enzyme defect, primary central nervous system deficiency of gonadotropin stimulus, and a defect in luteal cell steroidogenesis. The end result is

inadequate production of progesterone, but estrogen production is unimpaired.

Ovulation may occur, but the corpus luteum does not undergo its normal 10- to 12-day postovulatory regression. Thus, the corpus luteum activity may be prolonged, creating an excess of progestational activity. The resulting irregular bleeding has been called irregular shedding of the endometrium, the result of increased luteinizing hormone activity. Halban's disease may be the diagnosis if the corpus luteum persists longer than 16 days; this may result in ovarian cysts and abdominal pain, which suggest a possible ectopic pregnancy. Jones describes two responses to this prolonged corpus luteum activity,[7] a long, slow rise in estrogen or an abrupt rise with a prolonged progesterone level.

Persistent estrogenizing anovulatory cycling is more common. Anovulation without organic disease may be the result of primary ovarian dysfunction or may be secondary to neuroendocrine regulation of ovarian functions such as in polycystic ovary syndrome. Dysfunction at the hypothalamic level is the more common abnormality. Abnormal response may be related to diverse environmental and systemic influences.

In the adolescent, anovulatory cycling is most often associated with failure of the pubertal hypothalamic regulatory mechanisms for gonadotropin secretion to mature. Such maturation is initiated by body size, pineal, and neural factors. In early puberty, there is a noncyclic elaboration of steroid production, gonadotropin releasing hormone (GnRH), that stimulates production of follicle stimulating hormone (FSH) by the ovary, with resultant proliferative endometrial growth. Estrogen ultimately develops a negative feedback on the hypothalamus that reduces GnRH secretion. Alteration of the hypothalamus at puberty allows increasing pituitary FSH release, with resulting estrogen action on the endometrium. Unopposed continued production of estrogen with endometrial stimulation is the basic cause of anovulatory irregular bleeding in the adolescent. At midpuberty, new positive estrogen feedback effects develop which allow rapidly rising midcycle estrogen levels to trigger luteinizing hormone (LH). This leads to ovulation, the result of which is the secretion of progesterone and cyclic endometrial sloughing. If the new positive estrogen feedback fails to develop because of a delay in the maturation of this axis, the proliferative pattern persists, and there is persistent estrogenization and an anovulatory pattern of irregular bleeding.[8] This common pattern of adolescent anovulatory bleeding ends with maturation of the cyclic feedback mechanism. If it fails to mature, anovulation persists, the result being anovulatory endometrial sloughing. In the first year after menarche, 55% of cycles are anovulatory. It takes an average of 15 months to complete the first ten menstrual cycles. The adolescent pattern ends around the seventh postmenarcheal year and the usual menstrual cycle becomes 21 to 40 days, with the flow lasting from 3 to 8 days.[9] Although there is a greater than 50% incidence of anovulation immediately following menarche, only a small number present as gross irregular bleeding because of the large variation in acceptable pattern of menstruation.

In evaluating irregular patterns of uterine bleeding in the adolescent, a careful history is necessary. It is important to note the time of menarche, the interval between menstruation, the duration of flow, and the age at which thelarche and pubarche occurred. The patient should be examined for associated hirsutism, galactorrhea, and clinical evidence of endocrinopathy. The clinician should assess whether the ovaries are functioning, the absence of ovulation, and the patency of the genital outflow tract. The general physical examination and pelvic assessment are likely to be normal. A Pap smear is mandatory in patients who are sexually active and/or over 18. It often is useful to take a simple vaginal smear for cytology and to obtain the maturation index. Such a smear might suggest a diagnosis other than anovulatory bleeding. To complete the laboratory evaluation of any patient who has presumed anovulatory bleeding, thyroid hormone tests such as T4 and TSH, urinalysis, screening blood sugar, and a pregnancy test are necessary.

Teenagers who have had normal menstrual periods and later have heavy or prolonged menstrual flow should have a hematologic evaluation for bleeding diathesis. Therapy for bleeding diathesis should be directed at immediate control of the bleeding rather than at further endocrinologic evaluation.

In evaluating irregular bleeding, one of the most common problems that should be con-

sidered is pregnancy and its complications, such as threatened abortion, spontaneous or induced incomplete abortion, and ectopic gestation. Vaginal and cervical abnormalities and other sequelae of intrauterine exposure to DES also should be considered.

Idiopathic thrombocytopenic purpura and von Willebrand's disease are the most common bleeding diatheses of adolescence. In 1980, a 9-year case review by Claessens and Cowell examined all the admissions for acute menorrhagia at a children's hospital.[10] Pregnancy had been excluded. A primary coagulation defect was found in almost 10% of 59 patients, a figure that far exceeded what had previously been suggested. The coagulation disorders include idiopathic thrombocytopenic purpura, von Willebrand's disease, Glanzmann's disease (thrombasthenia),[11] thalassemia major, and Fanconi's anemia. Almost half of the patients presented with severe menorrhagia, defined by a hemoglobin of less than 10 gm%. The mean initial hemoglobin was 7.9 gm%. The majority of girls who had severe blood loss with their menstrual flow had coagulation disorders. It is therefore particularly important to rule out a coagulopathy when severe menorrhagia occurs at menarche. In addition to a careful history, with specific questions about easy bruising and any family history of bleeding diathesis, and a physical examination, the patient with menarcheal menorrhagia should have a blood smear and coagulation screen routinely. The coagulation screen should include prothrombin time, partial thromboplastin time, bleeding time, and a platelet count. These should be effective in ruling out all but the rarest hemorrhagic diathesis. In patients with severe bleeding, these tests should be done prior to a transfusion or hormonal therapy.

Gonadotropin testing should be done on patients with persistent anovulatory bleeding. Gonadotropins are released in a pulsatile fashion, with a cyclicity of approximately 90 minutes. It has been suggested that to show subtle changes three samples should be taken at 10- to 30-minute intervals. Equal volumes of serum from each sample may be combined and sent to the laboratory for more reliable and economic results. Prolactin measurement is mandatory in patients with oligomenorrhea and particularly in those that have progressed to amenorrhea. Prolactin is a most dynamic hormone, its levels are highest during sleep and the early hours of the morning and lowest in the most active hours. Prolactin levels vary slightly but not significantly throughout the menstrual cycle. Several drugs, especially amphetamines, antihypertensive drugs, anesthetic agents, and psychotropic drugs, may raise prolactin levels. In addition, stress, surgery, and stimulation of the chest wall and breast also may cause an elevation of prolactin levels.[12] Although the clinician should be aware of these normal physiologic variations in the prolactin pattern, a prolactin-secreting pituitary adenoma may be detected, nevertheless, with the finding of an elevated prolactin on a random sample because with a pituitary adenoma there is a loss of the normal sleep-induced elevation of prolactin and a decreased response to other prolactin-stimulating stimuli.

With normal levels of pituitary gonadotropins, the problem is hypothalamic dysfunction, whereas with an elevated FSH it may be premature ovarian failure or gonadotropin-resistant ovary syndrome. Decreased levels of FSH indicate possible hypothalamic-pituitary failure.[13] Thus, in taking the history it is important that the physician note any emotional disturbance and alteration of body weight that indicate a hypothalamic etiology.

Both hypothyroidism and hyperthyroidism may lead to anovulatory bleeding. Primary hyperthyroidism can provoke extremely heavy bleeding. Although the pathophysiology is not entirely understood, a derangement of the metabolic clearance rate of estrogen is suggested as the most likely cause.[14]

During the physical examination, any alteration of body fat and hair distribution should be assessed and discussed with the patient. In addition to evaluating pubertal development according to the Tanner staging, the breast examination should include a check for galactorrhea. Attention should be focused on ruling out early pregnancy, a common cause of irregular vaginal bleeding and the most common cause of secondary ameorrhea. Women with an erratic menstrual pattern can conceive without a preceding menstrual flow.

Laboratory data are designed to determine endocrine causes for the irregular bleeding, including pituitary, thyroid, and adrenal causes. Assays for thyroid stimulating hormone (TSH), FSH, LH, and prolactin should

be obtained. Those who show signs of defeminization or virilization should have an assay for serum cortisol, total testosterone, and DHEA-S (see Chapter 7).

The diagnosis of hypothalamic anovulation implies that the pituitary-ovarian system is operational and that the anovulation disturbances result from hypothalamic dysfunction. The most common etiology is psychogenic, usually stress or difficulty in coping. The patients have normal basal FSH and LH, but dynamic studies show a greater pituitary FSH sensitivity and reserve. Peripheral blood levels of estrogen and cortisol are compared to levels found in ovulatory women during the follicular phase. Basal levels of TSH and prolactin as well as response to GnRH are within normal limits. Hypothalamic dysfunction may result in loss of cyclicity, which leads to anovulation. The fact that appropriate counseling may bring about restoration of ovulatory menses is a clue that a suprahypothalamic dysfunction may be related to stress.

When irregular vaginal bleeding has progressed to amenorrhea, in addition to pregnancy one should consider anorexia nervosa, psychogenic-related stress, trauma, chronic renal disease, congenital adrenal hyperplasia, hyperthyroidism or hypothyroidism, and inflammatory bowel disease. There also are varying causes such as chronic anovulation syndrome (CAS) and premature ovarian failure, as well as uncommon entities such as the gonadotropin-resistant ovary syndrome.[15]

Drugs such as gonadal steroids and pharmacologic agents known to have an inhibitory effect on ovulation also can cause irregular bleeding. The latter include morphine, reserpine, phenothiazines, monoamine oxidase inhibitors, and anticholinergic drugs. Transient anovulatory intervals also may follow the discontinuation of oral contraceptives.

Emotional stress remains one of the most common causes of irregular vaginal bleeding in young women. Sheldrake and Cormack observed that 21% of students at Edinburgh University had irregular menstrual cycles.[16] Twenty percent of nursing students had oligomenorrhea, and almost 3% had secondary amenorrhea in extremely stressful environments (prisoners awaiting execution, concentration camp victims). However, less dramatic stress also can cause similar problems. Such irregular bleeding has been found in factory workers, military recruits, hospitalized patients, and nursing students.[17] In one study of 900 college students, 14.6% had menstrual disorders.[18] Oligomenorrhea and secondary amenorrhea were the chief complaints in 73%, which accounted for 10% of the total population of the school. Most had elevated levels of LH and normal-to-low levels of FSH, suggestive of CAS. This is significant because of its relation to two other clearly identifiable groups—those with hypogonadotropism associated with weight loss and those with normal gonadotropins considered to be hypothalamic in origin.

Chronic anovulation syndrome, defined by low FSH, elevated LH, and oligomenorrhea, is the most common and identifiable syndrome in young women with irregular vaginal bleeding. CAS was initially described in 1935 by Stein and Leventhal.[19] The patients in this initial study were sterile, amenorrheic, hirsute, and had palpably enlarged ovaries. The syndrome was found in 1.4% of a random population.[20] Elevated levels of LH and normal levels of FSH that are suggestive of this syndrome were found in 47.6% of adolescents with oligomenorrhea. Chronic anovulation syndrome represents an exaggerated example of a disturbed hypothalamic-pituitary-ovarian relationship. In this syndrome estrogen from the ovarian and peripheral sites interferes with FSH release but does not suppress the synthesis and release of LH. The altered FSH-to-LH ratio results in the classical ovarian changes with an increase in output of androstenedione and dehydroepiandrosterone, ovarian "prohormones." These hormones produce the clinical features—hirsutism and irregular vaginal bleeding—characterisic of the syndrome. The increased androgen content of the ovary produces follicular atresia. The ovarian prohormones also serve as precursors for peripheral conversion to estrone which increases LH production, thereby completing the cycle of abnormal hypothalamic feedback. Adolescent obesity may cause irregular bleeding because of emotional factors that may affect hypothalamic functioning. In addition, the sequestration of estrogens in the body fat of these girls alters the metabolic clearance rate of estrogen and may prevent the

surge of LH that is required for ovulation. The half-life of these stored hormones is approximately 10 hours.[21] Eventually, oligomenorrhea can progress to amenorrhea. Such amenorrhea occurs in girls whose breast and sexual development are normal.[22] In 75% of cases, this type of irregular bleeding and amenorrhea can be reversed by weight loss.[23]

Anorexia nervosa is an exaggerated example of the stress-related menstrual aberration. An estimated 1% of girls between 12 and 18 have anorexia nervosa, the onset typically occurring at 15. Boys also may be affected, but account for only 5–10% of all cases. As described by Lender et al,[24] the patient is preoccupied with all aspects of food, particularly calories. Misperception of body image and denial of illness, feelings of inadequacy, perfectionism, and obsessional thinking are primary psychopathologic features. The physiologic outcome of the starvation is hypoalbuminemia, resulting in inadequate amino acids to the liver and intravascular dilution. This accentuates the low serum albumin with an expanded plasma volume. Hypovitaminosis and hyperkeratinemia may be present. Anorexia nervosa usually is associated with hypogonadotropism, which leads to oligomenorrhea and ultimately secondary amenorrhea. Basal plasma LH and FSH levels are low, the decrease correlating with the degree of weight loss. The LH response to GnRH and clomiphene citrate is suppressed in 44% of cases; hypothalamic dysfunction is manifested as partial diabetes insipidus. Cortisol levels are normal, with loss of diurnal variation, and thyroxin levels are low normal. Thyroid stimulating hormone is normal. Plasma T_3 levels are low and thought to reflect a change in the peripheral metabolism of T_4 to T_3, with a reciprocal increase in the active form of T_3. Theories of explanation include a lesion of the ventromedial region of the hypothalamus and hyperactivity of the postsynaptic noradrenergic receptors in the ventromedial region of the hypothalamus.[24]

Such patients require expert nutritional therapy and psychiatric care. Initally, behavior modification is best done in a hospital; discharge is contingent upon reaching a predetermined weight. Although prognosis for the vast majority of patients is excellent, the serious form of the disease may be fatal.[24] (Anorexia nervosa is discussed in detail in Chapter 15.)

Extreme physical stress also may cause oligomenorrhea and amenorrhea. In a survey of 400 women on 25 college track and field cross-country teams, the frequency of amenorrhea correlated with the number of miles run per week. There was a dramatic increase in the incidence of amenorrhea in patients who ran 20 miles a week. Forty-five percent of those who ran 80 miles a week were amenorrheic. After a weekly 20 miles there was almost a straight-line increase. As mentioned earlier, secondary amenorrhea can result from excessive weight loss. Highly trained runners have a low percentage of body fat; however, weight does not seem to be correlated. For instance, endurance-trained swimmers tend to have a higher increase of body fat. An alternative explanation is the emotional stress incurred from arduous training and competition.[25,26] This oligomenorrhea and amenorrhea is in addition to athletic girls' reported delay in menarche.[27]

The apparent similarity beween patients with anorexia nervosa and obligatory runners was investigated by Yates et al.[28] Obligatory runners resemble anorexic individuals in terms of family background, socioeconomic class, and personality characteristics such as inhibited anger, extraordinarily high self-expectations, tolerance of physical discomfort, denial of potentially serious disability, and the tendency toward depression.

McArthur et al[29] examined amenorrheic athletes and found that the normal body composition of the amenorrheic athletes and the controls suggests that factors other than body weight or relative fat per se mediate the alteration of menstrual function. The authors suggested that an alteration in hypothalamic control of gonadotropin release that is independent of body composition plays a role in the development of athletic amenorrhea. The increased LH and simultaneous FSH pulse following the endorphin inhibitor naloxone indicate that athletic amenorrhea is at least influenced by endorphins. The authors concluded that the hypothalamus constitutes the locus of interference. It was suggested that stressful stimuli or situations that induce excesses of the endogenous opiate beta-endorphin also may induce certain habit

patterns. The habituation of jogging and long distance running suggests that stressful pathways may be habit forming.

For convenience's sake secondary amenorrhea may be divided into hypergonadotrophic and hypogonadotrophic types. Two types of hypergonadotrophic hypogonadism can be recognized, premature follicular depletion (premature menopause) and gonadotropin-resistant ovary syndrome.[30] Premature follicular depletion may be divided into those that are chromosomally normal and abnormal, such as mosaics of 45,X or 45,X/46,XY. Normogonadotrophic patients also may be found.

After measuring FSH, LH, and prolactin in the amenorrheic patients, a progesterone challenge test may be given. In the absence of elevated levels of prolactin, further evaluation for a pituitary tumor is usually unnecessary. Although there are sleep-induced rises in prolactin and some degree of menstrual cyclicity of prolactin, a random sampling of the hormone is sufficient because in hyperprolactinemic states, the physiologic variations are abolished. The classic technique for determining whether the amenorrhea's origin is the central nervous system–ovarian axis or lower genital tract is to do a challenge test with progesterone. Patients are either given an injection of 50 mg of progesterone in oil or 10 mg of oral medroxyprogesterone acetate for 10 consecutive days. If vaginal bleeding occurs after the administration and withdrawal of progesterone, adequate estrogenization of the endometrium has taken place. This eliminates the possibility of abnormalities of the outflow tract such as Asherman's syndrome. Other processes that may disrupt the endometrium such as genital tuberculosis may give similar findings. With failure to bleed, 2.5 mg of conjugated estrogen may be given daily for 25 days, with the addition of medroxyprogesterone acetate, 10 mg daily for the last 10 days. If withdrawal bleeding does not follow this regimen, there is an abnormality of the lower genital tract, whereas uterine flow indicates an abnormality of the ovary or the central nervous system pathways. The amenorrheic patient's inability to provide adequate stimulation is then assessed by measuring serum FSH levels. If the FSH is less than 5 mIU/ml there is a hypogonadotrophic state; this may be a hypothalamic or a pituitary dysfunction. If the FSH is greater than 40 mIU/ml, it is a hypergonadotrophic state, indicating either premature ovarian failure or gonadotropin-resistant ovary syndrome.

Occasionally the diagnosis is not clear. Because of the lack of reliable therapies, the routine screening of all oligomenorrheic patients may not be cost effective. However, in those who have vasomotor symptoms, or who want to become pregnant, a normal FSH level is insufficient to eliminate early ovarian failure. It has been emphasized by some authors that repeated determinations around the time the vasomotor symptoms occur may confirm the clinically suspected diagnosis of ovarian failure. The diagnosis of gonadotropin excess in the younger woman should be followed by determining a chromosome karyotype. Patients with 46,XY (Swyer's syndrome) or 45,X/46,XY karyotype have been reported to have pubertal development without virilization. Prior menstruation does not necessary mean that Y-chromatin material is absent. When Y-chromatin material is found, the patient should have gonadal extirpation because of the risk of neoplastic transformation. An ovarian biopsy should be considered in those with elevated gonadotropins and a 46,XX karyotype who desire pregnancy. It has been suggested that this can be done with the laparoscope. However, we believe an adequate ovarian biopsy can be accomplished only by open laparotomy. Such biopsies have not been valuable in determining response to ovulation induction in patients with premature follicular depletion. Many authors have attempted to induce ovulation in those with hypergonadotrophic hypogonadism by using menopausal gonadotropins. Although a rare pregnancy has been reported, most authors have failed to show any significant response.[31]

The gonadotropin-resistant ovary syndrome is characterized by primary or secondary amenorrhea before age 30, a normal chromosome complement of 46,XX, an increased endogenous production of FSH and LH, numerous morphologically normal, unstimulated follicles, and hypersensitivity of the ovarian follicles to excessive stimulation with exogenous gonadotropin.[32] In a series of such patients, the average age of onset was 14.

There was evidence of hypoestrogenization as shown by atrophic vaginal changes. The serum concentrations of estradiol were low. The biopsy findings in patients with gonadotropin-resistant ovary syndrome indicate an arrest following the early development of primordial follicles. Occasional antral formation appears here and in Kallman's syndrome (anosmic hypogonadotrophic hypogonadism). In Kallman's syndrome, FSH is biologically active as determined by bioassay, and there appears to be no genetic basis for the syndrome. The clinical presentation implies an acquired disease in the gonadotropin receptor. Although prolactin has been thought to exert an antigonadotropin action, elevated levels of prolactin have not been found in these patients.

Sporadic ovulatory cycles have been reported in women with gonadotropin-resistant ovary syndrome after a variety of treatments, which include wedge resection of the ovaries, dexamethasone suppression, and estrogen substitution therapy. Pregnancies occurred in two cases. The substitution of low dose estrogen is based on the hypothesis that it is capable of inducing FSH receptors in follicles. Whether the estrogen concentration achieved with replacement therapy is capable of inducing FSH receptors has not been verified. Other possible explanations of the beneficial effects of estrogen therapy on follicle stimulation include avoidance of down regulation after continuous exposure to high concentrations of gonadotropin and an increase in the biologic-immunologic ratio of endogenous gonadotropins.[33]

Retrospective reports of pregnancy following estrogen therapy leave many questions regarding its efficacy. Nonetheless, estrogen and progestin therapy is indicated to prevent metabolic changes resulting from estrogen deficiency. Estrogen replacement therapy has been strongly recommended in patients with ovarian failure of all etiologies.[34,35]

Nearly 10% of patients with premature ovarian failure have a mother or grandmother who had a similar problem.[35] This random positive family history indicates that premature oocyte depletion may be an inherited disorder. Family histories of patients with premature ovarian failure have suggested either an autosomal recessive or dominant inheritance. In several families, ovarian failure and neurocentric deafness have been reported, whereas in others apparently unique ovarian failure was associated with specific patterns of somatic abnormalities. In cases of inherited somatic anomalies associated with premature follicular depletion, a genetic etiology appears to be present.[36] An antibody to the cytoplasm of the ovum has been identified in serum, but its specificity has not been confirmed.[37]

The mere presence of ovarian IgG antibodies is not sufficient to implicate them as the cause of follicular depletion. Humoral antibodies generally are not cytotoxic. Another possible immunologic cause for ovarian failure is a functional LH agonist and LH receptor antagonist in serum from patients with premature ovarian failure syndrome.[34] It is hypothesized that excessive stimulation of ovarian follicles may lead to premature follicular depletion.

Other causes for premature ovarian failure include gonadal irradiation. Between 1500 and 3500 rads have been associated with amenorrhea. Chemotherapeutic agents also have been implicated in ovarian failure, but these results may be transient. Normal ovarian function may return as late as 2 years following drug exposure.

Infection also may be implicated in secondary amenorrhea. Approximately 5% of female patients who have mumps have gonadal involvement.[38] Systemic diseases such as mucopolysaccharidosis and galactosemia have been implicated. Pelvic inflammatory disease sufficient to cause chronic oophoritis results in menstrual dysfunction.

Asherman's syndrome is amenorrhea that results from the destruction of the endometrium following trauma. Although the condition usually occurs after an overzealous postpartum curettage, it may happen at other times. A typical pattern shows multiple intrauterine synechiae by hysterosalpingogram or hysteroscopy. Similar findings may be seen following endometrial tuberculosis, although this is rare in the United States. In recent years, the syndrome may occur following infection related to the intrauterine device. Asherman's syndrome is treated with dilatation and curettage (D&C) to disrupt the adhesions. There currently are advocates of the hysteroscope who claim that direct lysis may give better

results. In any event, the adhesions should be disrupted and some device inserted to prevent the opposing uterine walls from readhering. This may be done with a Foley catheter, an intrauterine device, or with a prosthesis constructed for such a purpose. In addition to mechanical lysis and the interposition of a prosthesis, the patient should be given high dose estrogens until some degree of endometrial sloughing occurs.

In all cases of secondary amenorrhea, the possibility of a prolactin-secreting pituitary adenoma exists. The prolactin-secreting adenoma is the most common of the pituitary tumors responsible for amenorrhea. Tumors less than 1 cm are microadenomas. The older classification of basophilic, acidophilic, and chromophobe adenomas is no longer useful. There is no demonstrated relationship between such adenomas and the use of estrogens or oral contraceptives. Computed tomography (CT) will reveal a pituitary adenoma in approximately one-third of patients with amenorrhea and galactorrhea. The amenorrhea associated with elevated prolactin levels appears to be the result of prolactin inhibition of the pulsatile secretion of GnRH. The pituitary glands in these patients respond to GnRH administration, indicating that the mechanism of amenorrhea is a decrease in GnRH secretion.[39]

Therefore, all patients with secondary amenorrhea—not just those with galactorrhea—should be screened by a serum prolactin level.[40] Patients with prolactin elevations should be followed with studies to visualize the pituitary. Polytomography may be used, although it is no longer efficient because it exposes the patient to high levels of radiation and is only 60% accurate. A coned-down view of the sella turcica may be used in the absence of more sophisticated methods that visualize the sella turcica. Enhanced CT is the most accurate and currently the most commonly accepted method for visualizing the pituitary. One should suspect a tumor in any patient who has a prolactin level above 40 ng/ml and be highly suspicious when the level is above 100 ng/ml.

A variety of tests are available to evaluate pituitary function when a pituitary adenoma has been found by CT and when there is a significant elevation of prolactin. These include the GnRH stimulation test, TRH stimulation test, and insulin tolerance test which measures response of prolactin, growth hormone, and cortisol. However, such tests rarely yield additional useful information, although there is some evidence that TRH stimulation or the growth hormone response to insulin-induced hypoglycemia may give some indication of pituitary reserve.[41]

The increased ability to detect pituitary tumor is accompanied by an improvement in surgical technique and better performance of transphenoidal resection. The ideal time for excision is when the adenoma is small, making an early diagnosis imperative. The transphenoidal approach results in complete resolution of hyperprolactinemia and resumption of cyclic menstrual periods in approximately 40% of patients with macroadenomas and 80–90% of those with microadenomas. Surgical failure may be the result of incomplete resection, multiple focal origins of the tumor, and continuing abnormality of the hypothalamus, which gives rise to chronic stimulation of the galactotroph. Radiation results are not as good as those of surgery because response is slow and hypopituitarism may occur as long as 10 years after therapy.

Bromocriptine is a pharmacologically available dopamine agonist that is being used more frequently in treating hyperprolactinemia of unknown cause and in the treatment of prolactin-producing pituitary adenomas. It is marketed as a 2.5-mg tablet. Absorption is rapid, but side effects such as vomiting may occur, the result of a central rather than local effect. The usual dosage is 2.5 mg, two or three times daily. Higher doses may be used as necessary. In many clinical trials, 80% of patients with amenorrhea and galactorrhea associated with hyperprolactinemia had normal restoration of menstruation.[42] The average treatment time to initiate a menstrual period is less than 6 weeks. An increasingly recognized problem with using Parlodel to treat an adenoma is the recurrence of symptoms and regrowth of tumor after the medication is discontinued. In one study, amenorrhea recurred in 41% of patients within 4 weeks after stopping treatment, and approximately 70% recurred within 6 weeks. Approximately 5% terminate treatment because of side effects.[43]

Bromocriptine has been increasingly used as premedication prior to resection of a pituitary

adenoma. It is expected that pretreatment will cause the tumor size to regress and become more circumscribed, making it easier to remove.

Irregular vaginal bleeding may be controlled by oral contraceptives. With irregular bleeding, it is best to use preparations containing 35 μg of estrogen. This may be increased to 50 μg if the original dose is ineffective. Although this amount of estrogen in oral contraceptives used for birth control is not advocated initially, it is quite proper when treating irregular uterine bleeding. The preparations with higher estrogen content are particularly recommended to control bleeding in adolescent patients. Failure to control hypermenorrhea with cyclic estrogen-progestin therapy suggests the possibility of an anatomic cause such as a myoma, polyp, or bleeding diathesis.

In anovulatory bleeding, it is feasible to substitute only the missing progestin. Progesterone or progestins are antiestrogenic when given in pharmacologic doses.[44] Progesterone induces an enzyme (17-hydroxysteroid dehydrogenase) that in endometrial cells converts estradiol to estrone. Progestins also diminish the estrogen effect on target cells by inhibiting augmentaiton of estrogen cytosol receptors that ordinarily modulate estrogen action. These influences account for the antimitotic, antigrowth impact of progestins on the endometrium. In the treatment of oligomenorrhea, withdrawal flow can be initiated by a progestational agent such as medroxyprogesterone, 10 mg daily for 10 days a month. If this regimen fails to induce bleeding, further evaluation is necessary. In the treatment of menometrorrhagia or polymenorrhea, progestins are prescribed for 10 to 14 days to induce stromal stability, which is followed by a withdrawal flow.

With an acute anovulatory bleeding episode, the bleeding may be controlled with a 35-μg estrogen progestin oral contraceptive. Therapy consists of one pill four times daily for 1 to 5 days. If this does not stop the flow, causes other than anovulatory cycling must be ruled out, including myomata, polyps, and complications of pregnancy such as incomplete abortion or ectopic pregnancy. If the flow diminishes significantly or abates predictably, the oral contraceptive should be continued once a day for the remainder of the 21-pill package, after which withdrawal flow will occur. The patient should be warned to anticipate a flow after therapy, and may continue on oral contraceptives if she desires contraception. Otherwise, the cyclic use of progestins for 10 days a month may be used to induce withdrawal flow.

Intermittent vaginal bleeding frequently is associated with low circulating estrogen levels which result in breakthrough bleeding. Under this circumstance, progestins do not control the bleeding. This is common in the adolescent patient in whom there has been prolonged anovulation leading to persistent desquamation, leaving little residual endometrial tissue. Estrogen therapy must be given prior to progestin. In acute and heavy bleeding, up to three doses of intravenous conjugated estrogen, 25 mg, may be given every 4 hours until bleeding stops.[45] After bleeding has stopped, a progestin must be substituted. In cases where the bleeding is less dramatic, estrogen-containing oral contraceptives or oral conjugated estrogens may be given. All estrogen therapy, however, must be followed by progestin.

One frequently encounters irregular bleeding secondary to the previous administration of Depo-medroxyprogesterone that had been taken to control the bleeding or as a contraceptive. Irregular bleeding occurs in 25% of those who take this medication. Cyclic estrogen in the form of conjugated estrogen, 2.5 mg daily for 7 days during the cycle, should control this bleeding.

Antiprostaglandins act upon the endometrial vasculature. The concentrations of PGE and $PGF_{2\alpha}$ increase progressively in the endometrium during the menstrual cycle. The prostaglandin synthetase inhibitors decrease menstrual blood loss.[46] This may result from altering the balance between the platelet proaggregating vasoconstrictor thromboxane and the antiaggregating vasodilator prostacyclin. Whatever the exact mechanism, prostaglandin inhibitors diminish menstrual bleeding in normal women as well as the bleeding of chronic endometritis secondary to IUDs.

Failure to respond to medical therapy usually occurs when progestins are used to control bleeding in patients with a hypoestrogenic or desquamated endometrium. Curettage is the last line of defense in anovulatory irregular bleeding in the adolescent patient and rarely

necessary, except in the patient with a known bleeding diathesis. Under these circumstances, bleeding should be controlled immediately by D&C, after which appropriate medical therapy should begin. If bleeding persists, one must suspect an anatomic abnormality not seen during the D&C. Further diagnostic evaluation such as hysterosalpingography or hysteroscopy should be considered.

The long-term prognosis for adolescents with irregular bleeding can be described as guarded at best. About 5% continue to have severe episodes of anovulatory bleeding and merit endocrinologic evaluation. The importance of continued follow-up is illustrated by a 60% rate of continued bleeding 2 years after its onset. Persistent problems are evident in 50% of patients after 4 years, and in 30% after 10 years.[47] Except in cases of blood dyscrasia, patients who had normal menses prior to irregular bleeding have a more favorable prognosis.[47]

Pelvic Pain in the Adolescent

The diagnosis of pelvic pain in the adolescent frequently is a clinical dilemma, and requires 6 or more months of persistent lower abdominal pain.[48] The problem often results in multiple visits to the physician's office by distraught parents attempting to find the cause of the pain. At the same time, the adolescent may use chronic pelvic pain as a way to attract attention, which makes it important that the physician assess interactions between the patient and her parents and siblings that could contribute to a psychologic cause.

The initial evaluation of pelvic pain requires a thorough history and physical examination. The history should include specific information regarding any gastrointestinal problems such as spastic colon or regional enteritis. When evaluating the genitourinary system, the clinician should look for evidence of recurring cystitis or gynecologic disorders such as persistent vaginal discharge, which may lead to upper and lower reproductive tract infections. The patient should be asked about dysmenorrhea during the history. Abnormal uterine bleeding is important in the overall assessment of pelvic pain because the discomfort may be secondary to heavy vaginal bleeding with clots. In addition, endomyometritis can be associated with pelvic pain and abnormal uterine bleeding. The pattern of pubertal development and problems associated with obstruction to the outflow tract, which may result in pelvic pain, also must be determined. Childhood diseases rarely cause pelvic pain; however, any infection such as mumps oophoritis also must be related in the history.[38] Table 6-1 list the differential diagnosis that should be included in pelvic pain assessment.

A general physical examination must be done. A pelvic examination should be done to determine if the pelvic area is tender or if there are any masses. A rectovaginal examination also is helpful if endometriosis is suspected; nodular areas along the uterosacral ligaments and cul-de-sac regions or cul-de-sac masses as with abscess formation may be discovered. The essential aspects of pelvic pain assessment are presented in Table 6-2.

The necessary laboratory tests are determined by the symptoms and pelvic findings. It may be necessary to radiologically assess the gastrointestinal (GI) tract, i.e., upper GI, small

Table 6-1. Causes of Acute and Chronic Abdominal Pain in the Adolescent.

Hematometra
Intussusception
Peritonitis
Perforation of a viscus
Urinary calculus
Hematosalpinx
Pelvic inflammatory disease
Imperforate hymen
Vaginal septum
Blind pouch of the vagina with hematometra and hematocolpos
Ectopic pregnancy
Chronic pancreatitis
Regional enteritis
Meckel's diverticulum with abscess
Ulcerative colitis
Constipation
Urinary tract infection
Porphyria
Sickle cell anemia
Mesenteric lymphadenitis
Hydronephrosis
Liver cysts (oral-contraceptive related)
Bowel obstructions
Splenomegaly
Neuroblastoma
Urachal cysts

Table 6-2. Pelvic Pain Assessment in the Adolescent.

1. Rule out any significant pelvic pathology.
2. Perform a careful pelvic examination, including a recto-vaginal exam.
3. Emphasize the importance of a thorough history.

bowel follow-through, and a barium enema and gallbladder series if the pelvic pain is associated with specific GI symptoms. In addition, sigmoidoscopy may be indicated if there is evidence of lower GI tract symptoms such as hematochezia.

Diagnostic laparoscopy is an integral part of the assessment of pelvic pain in this age group. Goldstein et al[49] used laparoscopy to examine 109 adolescent girls between 10.5 and 19 who had unexplained chronic pelvic pain. Forty-nine patients (45%) had endometriosis, the most common finding, while 17 (16%) had postoperative adhesions, and 10 (9%) had congenital anomalies of the uterus. Moreover, pelvic inflammatory disease with adnexal adhesions was found in 9%, chronic hemoperitoneum in 5%, functional ovarian cysts in 5%, and uterine-related abnormalities in 2%. No pelvic abnormality was found in ten patients(9%).

The psychiatric aspects of chronic pelvic pain have been evaluated by Gross et al,[50] in a multidisciplinary study of 25 gynecologic patients. While each patient had a normal pelvic examination, a psychiatric assessment found the most frequent diagnosis was "significant pathology with boderline syndrome, and hysterical character disorder." A significant incidence of early childhood family dysfunction and incest also was noted. Psychologic testing corroborated the high incidence of psychopathology. Differences between organic and psychogenic functional pelvic pain have been found.[48] Organic pain frequently is sharp, crampy, waking the patient at night, and has intermittent radiation, whereas psychogenic pain is usually absent during sleep. Some authors suggest that women with chronic pelvic pain are psychiatrically disturbed. The onset of pelvic pain can be linked to a stressful event or life crisis.

Treatment of chronic pelvic pain often involves reassuring the patient that there is no pelvic pathology. The adolescent must be apprised of the role of stress in her pain, and she must be allowed to freely express her anger and frustration.

Acute abdominal pain in the adolescent can have any one of a number of etiologies (Table 6-1). Particular attention should be paid to signs of acute appendicitis and torsion of an adnexa, more commonly found on the right side. Mittelschmerz also must be considered in the differential diagnosis; this is typically characterized by midcycle acute abdominal pain. The pain associated with mittelschmerz is ephemeral and associated with leakage of fluid from the ovary around the time of ovulation, resulting in peritoneal irritation. A ruptured corpus luteum also is seen in this age group; these patients present with acute abdominal pain and evidence of intraabdominal hemorrhage. Dysmenorrhea, either primary or secondary, also must be considered. These problems are discussed in Chapter 13. Acute

Table 6-3. Center for Disease Control Criteria for Toxic Shock Syndrome.

1. Fever (temperature > 38.9° C[102° F])
2. Rash (diffuse macular erythroderma)
3. Desquamation, 1 to 2 weeks after onset of illness, particularly of palms and soles
4. Hypotension (systolic blood pressure < 90 mmHg for adults, or < 5th percentile by age for children < 16 years of age, or orthostatic syncope)
5. Involvement of three or more of the following organ systems:
   A. Gastrointestinal (vomiting or diarrhea at onset of illness)
   B. Muscular (severe myalgia or creatine phosphokinase level > 2 × ULN[a])
   C. Mucous membrane (vaginal, oropharyngeal, or conjunctival hyperemia)
   D. Renal (BUN[b] or CR[c] > 2 × ULN or > 5 white blood cells per high-power field—in the absence of a urinary tract infection)
   E. Hepatic (total bilirubin, SGOT,[d] or SGPT[e] > 2 × ULN)
   F. Hematologic platelets < 100,000/mm^3
   G. Central nervous system (disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent)
6. Negative results on the following tests, if obtained:
   A. Blood, throat, or cerebrospinal fluid cultures
   B. Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

[a]Twice upper limits of normal for laboratory.
[b]Blood urea nitrogen level.
[c]Creatinin level.
[d]Serum glutamic oxaloacetic transaminase level.
[e]Serum glutamic pyruvic transaminase level.

abdominal pain as a result of cystitis is common in the child or adolescent and can be associated with trauma to the urethra, including contusion to the urethral meatus, which provides a pathway for bacteria to enter the bladder and produce cystitis. Infection of the reproductive organs also must be considered when assessing the adolescent patient with abdominal pain. The presentation and clinical course of infectious problems in the reproductive organs is addressed in Chapter 17.

Establishing the diagnosis of acute pelvic inflammatory disease (PID) in the adolescent may require a diagnostic laparoscopy. Kleinhaus et al[51] diagnosed acute PID in 28 of 50 patients. Preoperative diagnosis was correct in 15 of 32 patients. The label "chronic PID" frequently is misleading and should not be determined solely by physical examination.

Toxic shock syndrome also must be considered in the differential diagnosis of abdominal pain. This often is associated with other signs and symptoms, as noted in Table 6-3.

Endometriosis

Endometriosis is a condition in which endometrial tissue occurs aberrantly, implanting or infiltrating various locations throughout the pelvis. One of the first recorded cases is mentioned in the Egyptian papyrus of 1600 B.C.[52]

Although usually confined to the pelvis, endometriosis reportedly has been found in the bladder,[53] pleura,[54] subarachnoid space and muscles,[55] and even in the lungs.[56] It should be considered when an adolescent female presents with pelvic pain. Goldstein et al[57] reported a 47% incidence of endometriosis in adolescent patients (10.5–19.25 years of age) evaluated for both cyclic and acyclic chronic pelvic pain. They noted the onset of pain occurred, on the average, 2.9 years after menarche. Chatman and Ward[58] prospectively evaluated 43 consecutive laparoscopies done on black adolescents and found a 65% incidence of endometriosis.

Symptoms associated with endometriosis include irregular menses, gastrointestinal and bladder problems, and increased vaginal discharge. The most common finding on pelvic examination is cul-de-sac tenderness with or without nodularity. Seventeen percent in the series of Goldstein et al had normal pelvic exams.[57] The endometrial implants are not always the typical brownish "powder burn" type, but may appear to be hemorrhagic areas; thus 20% of the lesions were not recognized grossly as typical, but were confirmed histologically.[57]

Although laparoscopy is the way to diagnose endometriosis, it is not without its dangers, i.e., a death rate of one in 44,000[59] and the risk of major complications in 5.4 of every 1000 procedures.[60]

Gastrointestinal, uterine, and genitourinary tract anomalies have been noted in adolescents with endometriosis.[61] An ovarian cyst (endometrioma) may present as an abdominal mass in adolescents with endometriosis.[62] This possibility must be considered in evaluating even the premenarchal adolescent. An imperforate hymen or vaginal septum, with subsequent accumulation of hematocolpos, hematometra, and endometriosis can cause a subsequent endometrioma. The experience at the University of Louisville with endometriosis associated with a uterine anomaly may represent a different teleologic entity than endometriosis associated with infertility because complete remission of the condition occurred when the uterine-vaginal defect is corrected.

A 12-year-old white female admitted to Kosair-Children's Hospital, Louisville, Kentucky, on December 12, 1978, had menarche when she was 10. A second menstrual flow occurred 1 month later. Both menses were characterized by 3 days of vaginal spotting. The last flow was followed by the sudden onset of right lower quadrant pain. A little more than 2 weeks later she was admitted for evaluation.

Findings on physical examination included an abdomen without palpable masses; tenderness in the right lower quadrant, but with no rebound; a midline mass consistent with a uterus and a mass involving the right adnexa revealed by rectal exam; a vaginal transverse band immediately adjacent to a nulliparous-appearing cervix; and a fixed and retroverted uterus.

Laboratory data included an intravenous pyelogram and barium enema, both of which were normal. On December 18, 1978, the patient under anesthesia underwent vaginoscopy, laparoscopy, and colpotomy, with the creation of a vaginal window into an apparent hematocolpos. At that time, vaginoscopy revealed a second cervix within

the blind pouch of the vagina. Diagnostic laparoscopy revealed extensive unilateral (right) endometriosis. The vaginal window subsequently closed, and 4 months later the patient again presented with acute abdominal pain of a cyclic nature. She was readmitted for a second vaginal window. Subsequent dilatation of the vaginal window was done in an effort to prevent closure. The vaginal window, however, closed again, and the patient underwent an exploratory laparotomy on March 10, 1980, during which a right uterine horn, cervix, fallopian tube, and ovary were removed and a vaginal cuff created for drainage. At that time the endometriosis was completely gone. The pathology report revealed a right rudimentary horn consistent with a didelphic uterus with endocervicitis, endometritis, and acute adnexal inflammation. No evidence of endometriosis was found. The patient did well as noted at a postoperative follow-up 1 year later.

Uterine anomalies frequently are associated with renal agenesis on the affected side.[61] Endometriosis frequently is a chronic process that begins at menarche and may be enhanced by mechanical obstruction (imperforate vaginal septum or congenital atresia of the cervix).[62] Fallon hypothesized that endometriosis tends to develop after 5 or more years of continued menses without pregnancy.[63]

Etiology of Endometriosis

First described as a specific disease in 1860 by von Rokitansky,[64] the etiology of endometriosis even today is not clearly defined. Sampson[65,66] hypothesized that retrograde menstruation was a cause. However, this theory was challenged by Novak,[67] who believed that menstrual discharge is necrotic, autolyzed, and incapable of regeneration.

Markee[68] evaluated the ability of aberrant endometrium to proliferate by demonstrating the development of endometrial tissue in the anterior chamber of the eye. TeLinde and Scott[69] gave Sampson's theory further support when they successfully diverted uterine menstrual efflux into the peritoneal cavity. However, Heim[70,71] and Hartman[72] were unable to produce endometriosis from endometrial cells placed in the peritoneal cavity of humans and monkeys. Other theories on the etiology of endometriosis include "imitational metaplasia," i.e., transplanted endometrial cells stimulate metaplasia in tissues derived from coelomic mesenchyme;[73,74] and Meyer's hypothesis that totipotential mesothelium stimulated by recurring menstrual insults undergoes metaplasia into functional endometrium. Table 6-4 provides further information regarding endometriosis in adolescents.

Pattern of Inheritance of Endometriosis—Genetic Aspects

Simpson et al[91] postulated a polygeneic/multifactorial pattern of inheritance with a 6.9% recurrence risk for first-degree relatives. Seventy-six percent of 113 patients (18–65 years old) had histologically diagnosed endometriosis. Menorrhagia may be a predisposing factor to endometriosis,[92] in that clots enhance retrograde menstruation. Fifty-seven percent had associated dysmenorrhea, 26% dyspareunia, and 30% metrorrhagia. Oral contraceptives are thought to provide prophylaxis against endometriosis.[92]

Normal estrogen levels are reported in patients with endometriosis.[93] Selensky and Liu[92] hypothesized that endometriosis may be caused by an increased sensitivity to estrogens.

Who Should Be Evaluated?

Not everyone with dysmenorrhea needs to be evaluated for endometriosis. Patients who should undergo evaluation are those presenting with uterosacral nodularity and progressive dysmenorrhea that does not yield to the standard methods of treatment—nonsteroidal, antiinflammatory agents (NSAID), prostaglandin synthetase inhibitors, or ovulation suppressive agents (oral contraceptives). The latter treatment has an 80% subjective response rate.[94] Androgens also have been prescribed for endometriosis.[95] Pregnancy is an effective therapy,[96] but the effects are not predictable, as symptoms of endometriosis increase in the first trimester and decrease during the third trimester.[96] Meigs[97] has said that pregnancy at an early age is a prophylactic measure in preventing endometriosis.

TeLinde[98] has recommended that younger patients have surgery early in the course of their disease so that future fertility can be preserved.

Table 6-4. Endometriosis in Adolescents.

Author(s)	Findings
Schifrin et al[76]	Fifteen cases of endometriosis in patients 12 to 20 years old and presenting with epigastric pain, lower quadrant abdominal pain, or dysmenorrhea. There was an associated increased incidence of GI and GU anomalies.
Fallon[63]	Four percent of teenage females (nine of 225) had endometriosis. Four of the 9 had endometriosis at the time of preoperative diagnosis of acute appendicitis.
Derryberry and Bonney[77]	Endometrioma in a 15-year-old black with a normal vagina and introitus, and a stenotic cervical isthmus.
Bullock et al[78]	Symptomatic endometriosis in teenagers. Wilford Hall, USAF Medical Center, four cases, 17 to 19 years old.
Meigs[79]	Endometrial cysts in 13- to 19-year-old adolescents.
Hanton et al[80]	Sixty-eight young patients (63 had menarche 5 to 10 years before the diagnosis, and 6 had congenital obstruction to menstrual flow) in a 30-year review of cases at the Mayo Clinic.
Hanton et al[81]	Case report of endometriosis associated with complete or partial obstruction of menstrual egress.
Moore et al[82]	Seven of 127 patients with ovarian masses had endometriosis; age range, birth to 17.
Bruser[83]	Appendectomy with inability to relieve symptoms. Twelve patients, 19 to 31 years old. Subsequently each was found to have endometriosis.
Depp and Pope[84]	Of 233 patients between ages 10 and 19, 2.3% had endometriosis.
TeLinde[85]	Of 8789 pelvic laparotomies, 1.2% had microscropically diagnosed endometriosis within 10 years of menarche.
Sutton[86]	A 14-year-old with imperforate hymen, hematocolpos, hematometra (bilateral hematosalpinges), and peritoneal implants.
Sutton[87]	Etiologic factors in endometriosis—case of reflux menstruation with a bicornuate uterus. Intensely distended left horn.
McDonald[88]	Endometriosis associated with didelphic uterus.
Mittal et al[89]	Endometriosis of the appendix, presenting as acute appendicitis. Patients were 14 to 62 years old. Forty percent (20 of 50) incidence of GI tract involvement with endometriosis.
King[90]	Metastatic endometriosis in abdominal scars of a 17-year-old female. Pain and tenderness in the right lower abdominal quadrant with a preoperative diagnosis of acute appendicitis.

Table 6-5. Prostaglandins and Endometriosis.

Authors	Findings
Willman et al[99]	Endometriosis associated with increased prostaglandin content.
Meldrum et al[100]	Increased peritoneal fluid prostaglandin $F_{2\alpha}$.
Schenken et al[101]	Increased peritoneal fluid prostaglandin $F_{2\alpha}$, rabbit.
Drake et al[102]	Increased peritoneal fluid volume and increased prostaglandin metabolites (thromboxane B_2, 6-ketoprostacyclin $F_{1\alpha}$).
Badawy et al[103]	Peritoneal fluid revealed wide variation of prostaglandin E_2 and $F_{2\alpha}$ metabolites. No correlation between the stage of endometriosis and the concentration of prostaglandin E_2 or 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM). No correlation between the concentration of PGE_2 and $PGF_{2\alpha}$ metabolites during different parts of the cycle.
Haney et al[104]	Increased macrophages in the peritoneal fluid and increased peritoneal fluid volume with endometriosis.

Endometriosis and Prostaglandins

There may be a correlation between endometriosis and an alteration of prostaglandin secretion and metabolism. It is undetermined, however, whether the effect of endometriosis on prostaglandin function is related to either the etiology or the mechanism of action of endometriosis in both the adolescent and adult patient. Further information regarding prostaglandins and endometriosis is presented in Table 6-5.

Modalities of Treatment

Danazol (isoxazol derivative of ethinyltestosterone) is an effective treatment for endometriosis. In a series of 39 patients with laparoscopic biopsy–proven endometriosis, treatment with 800 mg danazol for an average of 6 months resulted in a marked decrease of endometriosis: 59% showed no evidence of the disease.[105] Twenty-six percent had peritoneal adhesions and hemosiderin deposits but no active endometriosis. Residual endometriosis was noted in 15%. Severe endometriosis may require up to 18 months of therapy. Dmowski and Cohen recommend danazol doses of 800 mg daily for 3 to 18 months, depending upon the degree of disease.[106]

Table 6-6. Classification of Pelvic Endometriosis by Acosta et al.[107]

Classification	Characteristics
Mild	Scattered, fresh lesions (i.e., implants not associated with scarring or retraction of the peritoneum) in the anterior or posterior cul-de-sac or pelvic peritoneum. Rare surface implant on ovary, with no endometrioma, without surface scarring and retraction, and without periovarian adhesions. No peritubular adhesions.
Moderate	Endometriosis involving one or both ovaries, with several surface lesions, with scarring and retraction, or small endometriomas. Minimal perivoarian adhesions associated with ovarian lesions. Minimal peritubular adhesions associated with ovarian lesions. Superficial implants in anterior and/or posterior cul-de-sac with scarring and retraction; some adhesions, but no sigmoid invasion.
Severe	Endometriosis involving one or both ovaries (usually both) with endometrioma $> 2 \times 2$ cm. One or both ovaries bound by adhesions associated with endometriosis, with or without tubal adhesions to ovaries. One or both tubes bound or obstructed by endometriosis; associated adhesions or lesions. Obliteration of the cul-de-sac from adhesions or lesions associated with endometriosis. Thickening of the uterosacral ligaments and cul-de-sac lesions from invasive endometriosis with obliteration of the cul-de-sac. Significant bowel or urinary tract involvement.

Endometriosis has been classified according to Acosta et al[107] (Table 6-6), as well as by the American Fertility Society[108] (see Table 6-7).

Danazol appears to be the treatment of choice for endometriosis. Its effects are presented in Table 6-8.

Conclusion

Abnormal vaginal bleeding may begin at menarche. Under such circumstances, coagulopathy should be strongly considered. If menstruation occurs at irregular intervals and

Table 6-7. American Fertility Society Classification of Endometriosis.[108]

Location		Characteristics		
Peritoneum				
Endometriosis		< 1 cm	1-3 cm	> 3 cm
		1	2	3
Adhesions		Filmy	Dense with partial cul-de-sac obliteration	Dense with complete cul-de-sac obliteration
		1	2	3
Ovary				
Endometriosis		< 1 cm	1-3 cm	> 3 cm or ruptured endometrioma
	R	2	4	6
	L	2	4	6
Adhesions		Filmy	Dense with partial ovarian enclosure	Dense with complete ovarian enclosure
	R	2	4	6
	L	2	4	6
Tube				
Endometriosis		< 1 cm	> 1 cm	Tubal occlusion
	R	2	4	6
	L	2	4	6
Adhesions		Filmy	Dense with tubal distortion	Dense with tubal enclosure
	R	2	4	6
	L	2	4	6

Stage I, mild (1-5); Stage II, moderate (6-15); Stage III, severe (16-30); Stage IV, extensive (31-54).
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is characterized by heavy flow, hormonal therapy frequently alleviates the problem.

When faced with the clinical problem of pelvic pain in the teenager, one should use a systematic differential diagnosis with special attention to the possibility of endometriosis. With prompt diagnosis and medical management the adolescent should no longer fear menstruation and should function normally throughout the menstrual cycle.

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Table 6-8. Effects of Danazol.

Parameter	Effect
Gonadotropins	
Basal	NC[109] or ↓[110]
Midcylce surge	↓[111]
No compensatory increase in FSH and LH in castrated animals[112]	
Prolactin	NC[113]
Sex steroids	
Testosterone	↓[114]
Androstenedione	↓[114]
Progesterone	←[115]
DHEA	←[115]
Shortening of the luteal phase[116]	
Binding globulins	
SHBG	↓[117–119]
CBG	↓[118]
TBG	↓[120]
ALB	↓[121]
GnRH response	NC[109] or ←
Cholesterol	NC[122]
HDL	↓[122]
LDL	NC[122]
VLDL	NC[122]
Sex steroid receptors	
Androgen	←[123]
Progesterone	←[123]
Estrogen	← or no significant binding[123–126]

Side effects
- Acne, increase in skin oiliness
- Hirsutism
- Edema
- Weight gain
- Decrease in breast size
- Muscle cramps
- Paresthesias
- Alopecia skin rash (capsule dye)
- Cholestatic jaundice
- Clitoral hypertrophy (rare)
- Clitoromegaly—in utero exposure

Dosage
1. 800 mg daily in two divided doses (adult weight).
2. Variable dosage beginning with 800 mg and decreasing, correlated with presence of amenorrhea.[127]

NC, no change; ←, normal; ↑, increased levels; ↓, decreased levels.

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Androgens in the Adolescent 7

Robert Wild

Adolescence is a time of unrest. Body image and peer interaction are critical to the evolving personality. In a society where the media is constantly promoting certain physical attributes, the adolescent is pressured to look perfect. Obesity, hirsutism, and acne can thwart what is often an unobtainable goal. It therefore behooves all health professionals who treat adolescents to understand abnormal androgen dynamics as found in patients with polycystic ovarian syndrome (PCOS). Intervention may prevent major health problems and can contribute to psychological well-being.

Definition of Terms

Polycystic ovaries are a sign, not a diagnosis. They may be found in association with a number of endocrinopathies. Polycystic ovary syndrome has great biochemical and clinical variability. Anovulation, infertility, hirsutism, obesity, and bilateral polycystic ovaries are associated with a number of endocrine disorders that include hyperthecosis, androgen-secreting tumors, Cushing's syndrome, hypothyroidism, chronic anovulation with hyperprolactinemia, congenital adrenal hyperplasia, and certain CNS tumors. As described by Merrill,[1] polycystic ovaries are a normal finding in the evolution of a mature hypothalamic-pituitary-gonadal axis.

Because antral follicles are formed, the small prepubertal ovary is normally polycystic. However, ovulation does not occur because of inadequate stimulation of the component cellular elements of the ovarian follicle.[2] A similar pattern is found in the ovaries of some girls and young women who have functional or hypothalamic amenorrhea when there is incomplete follicular maturation and ovulation as a result of inadequate and/or inappropriate gonadotropin stimulation. As a result of inadequate luteinizing hormone (LH) stimulation, these polycystic ovaries are not androgen producing.

For purposes of this discussion of the dynamics of androgens, we will define PCOS as a nontumorous, dysfunctional condition of the ovary in which there is LH-dependent hypersecretion of androgens from the hyperplastic theca and stromal cells.

The Polycystic Ovary Syndrome (PCOS)

Menstrual disorders associated with hirsutism, acne, or obesity indicate the likelihood of polcystic ovarian syndrome.[3,4] The case histories of many patients with PCOS indicate its onset in adolescence.[5] Several cases of PCOS have been diagnosed within the perimenarchal period.[6,7] When systematically evaluated in the adolescent its prevalence is surprisingly high, not only in patients with menstrual disorders, acne, or obesity, but also in some who show no symptoms or signs of hyperandrogenemia.[8,9] PCOS now is considered to consist of a spectrum of disorders characterized by functional ovarian hyperandrogenism:[10] in the more severe cases patients tend to have anatomically large polycystic ovaries,[11] or hyper-

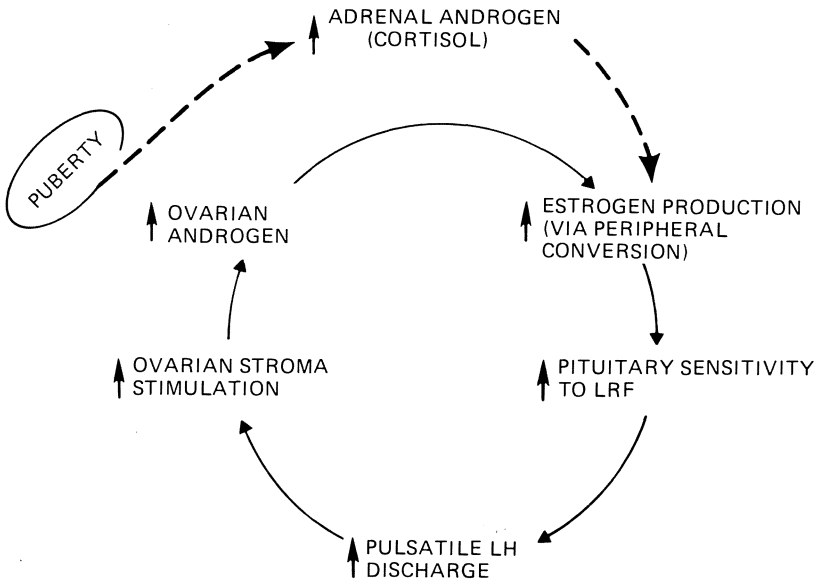

Figure 7-1. Proposed mechanism for the perimenarchal onset of polycystic ovarian syndrome. Reproduced with permission from James VHT: Functional aberrations of the hypothalamic-pituitary system in polycystic ovary syndrome: a consideration of the pathogenesis. In James VHT, et al (eds): Endocrine Function of the Human Ovary. Copyright 1976 by Academic Press Inc. (London) Ltd.

thecosis;[12] in milder cases no histologic abnormality is found.[13]

Pathogenesis of PCOS

The dynamics of normal adrenarche have been discussed in Chapter 2. Briefly, it remains an open question whether adrenarche is a consequence of changes in the adrenal responsiveness to adrenocorticotrophic hormone (ACTH)[14,15] or is secondary to a postulated separate adrenal androgen stimulating hormone (AASH)[16,17] that acts in conjunction with ACTH. It is hoped that with the surge of interest in the processing of the parent molecule of ACTH (proopiomelanocorticotropin or POMC)[18] that this fascinating mystery can be enlightened.

Adrenal androgens not only actively contribute to secondary sex characteristics, but may directly affect skeletal maturation and growth.[19]

Obese prepubertal children and those at Tanner stage P_1 of puberty have plasma levels of adrenal and Δ_5 and Δ_4 steroids that are higher than those found in normal children at the same stage of sexual maturation.[20]

Yen postulates that adrenal androgens are an important contribution to the perimenarchal onset of PCOS (Fig. 7-1).[5]

An exaggerated adrenarche with adrenal androgen excess could result in inappropriate nonovarian estrogen production. This disorder might be self-limiting were it not for acyclic estrogen production (via peripheral conversion of adrenal androgens) that induces inappropriate gonadotropin secretion. This, in turn, affects the ovary, causing an overproduction of ovarian androgens. Thus the androgenic basis for the inappropriate estrogen feedback is eventually shifted from the adrenal to the ovary, although an adrenal contribution to androgen excess may continue and combine with ovarian sources in PCOS patients. Emotional stress at puberty as well as obesity per se are associated with increased adrenal activity.

Pathophysiology of Chronic Anovulation in PCOS

A major characteristic of PCOS is chronic anovulation. Elevated urinary LH was one of the first abnormal hormonal findings documented in PCOS.[21] This early work used bioassay methodology which relied on specific

radioimmunoassays for plasma LH and follicle stimulating hormone (FSH) to confirm the elevated LH secretion.[22] Low or low-normal FSH plasma levels were found and did not exhibit the erratic fluctuations characteristic of LH.

It has been suggested that a common biochemical feature is a disturbance in the dynamics of androgen-estrogen conversion. The cyclic changes in ovarian estrogen that are normally responsible for appropriate feedback regulation of cyclic gonadotropin release are overruled by a constant outpouring of estrogen from extraovarian sources. Thus, the secretion of excessive amountts of androgen and its subsequent peripheral conversion to estrogen form the basis for the development of chronic anovulation in PCOS.

Inappropriate Gonadotropin Secretion

Except for the midcycle LH surge, PCOS patients' LH levels are usually higher than those in normally cyclic women. The elevated LH secretion results from an increased frequency and/or amplitude of the secretory pulse of LH.[23] A normal plasma LH occasionally may be found, but LH levels are erratic in PCOS and with frequent sampling the average level is usually elevated. Rarely are normal LH levels sustained and the LH-to-FSH ratio usually is abnormally high.

The low FSH level in PCOS patients may reflect both the known increased sensitivity of the inhibition of FSH secretion by estrogens and the relative insensitivity of the response of FSH to gonadotropin releasing hormone (GnRH). Since an inhibinlike material that depresses FSH secretion is present in antral fluid, the lowered FSH secretion could be due to increased folliculostatin (inhibin).[24] Regardless of whether the increased LH-to-FSH ratio or the hyperandrogenism is the primary event, one reinforces the other, producing an unending circle of hormonal and ovarian follicle abnormalities that cause chronic anovulation (Fig. 7-2).[25]

The Polycystic Ovary

The observation of polycystic ovaries has the same general nonspecific diagnostic connota-

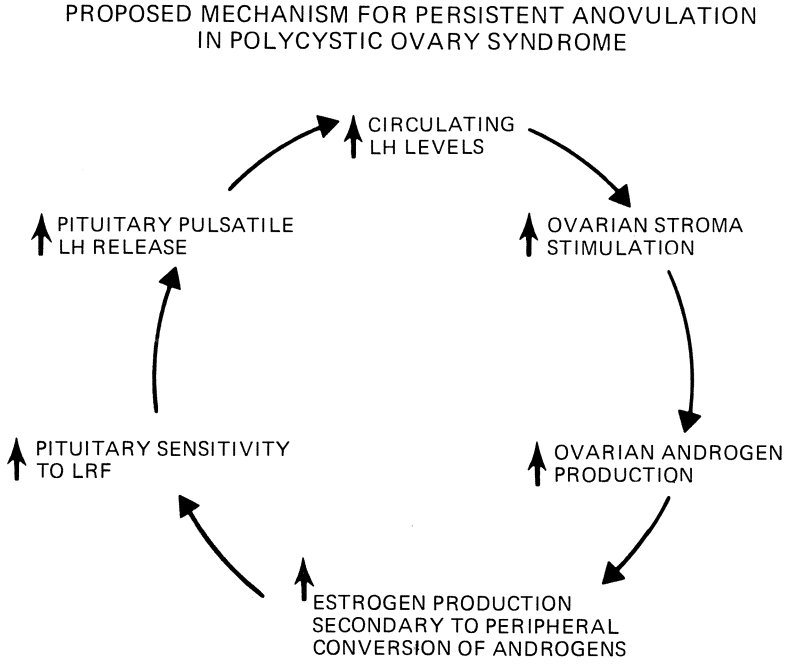

Figure 7-2. Proposed mechanism for persistent anovulation in the polycystic ovarian syndrome. Reproduced with permission from James VHT: Functional aberrations of the hypothalamic-pituitary system in polycystic ovary syndrome: a consideration of the pathogenesis. In James VHT, et al (eds): Endocrine Function of the Human Ovary. Copyright 1976 by Academic Press Inc. (London) Ltd.

tion as an "enlarged heart." The polycystic ovary reflects chronic oligoanovulation as a result of delayed or deranged follicular maturation. Follicular maturation and atresia are finely balanced physiologic events controlled by inhibitory and stimulatory factors that are elaborated both externally and internally in the follicle. Among those factors are the hormones LH, FSH, prolactin, estrogens, androgens, and insulin. Proper sequencing and interplay of these controlling substances are necessary for normal folliculogenesis.

The dominant follicle destined for ovulation is primarily an estrogen-producing organ. Estrogen biosynthesis by the follicles is most efficiently accomplished through a cooperative effort of theca and granulosa cells.[26] This forms the basis for the so-called "two-cell theory" of estrogen production.[27] According to this concept, the thecal compartment of the follicle synthesizes androgens (primarily androstenedione in response to LH, which then diffuses into the granulosa compartment where the aromatase enzyme converts androgens to estrogens under the influence of FSH) (Fig. 7-3).[28]

There are myriad other modifying factors that influence follicular development.[29] For example, recent data indicate that insulin potentiates the effect of LH on the theca cells' steroid synthesis.[30] The production rate of progesterone and androstenedione by theca cells is enhanced under in vitro conditions with the addition of insulin to the incubating medium.[30] This observation gives possible insight into the relationship between insulin resistance, hyperinsulinemia, and hyperandrogenism in females.

A fundamental principle of follicular maturation is self-enhancement. Estrogen secretion further potentiates the effect of FSH on granulosa cells, permitting increased estrogen production. Suboptimal androgen aromatization leads to androgen excess, which also is characterized by self-enhancement.[31]

Androgens produced by theca cells under the influence of LH increase the rate of atresia, which adds more theca cells to the pool that is capable of secreting androgens. Thus, the polycystic ovary reflects the steady state leading to the excessive secretion of androgens. Histologically, the ovary is characterized by a smooth and thickened capsule and multiple follicular cysts surrounded by abundant ovarian stroma. The subcapsular cysts are lined with a reduced number of granulosa cells, early antrum formation, and hyperplasia of the theca interna with luteinization (Figs. 7-4–7-6).

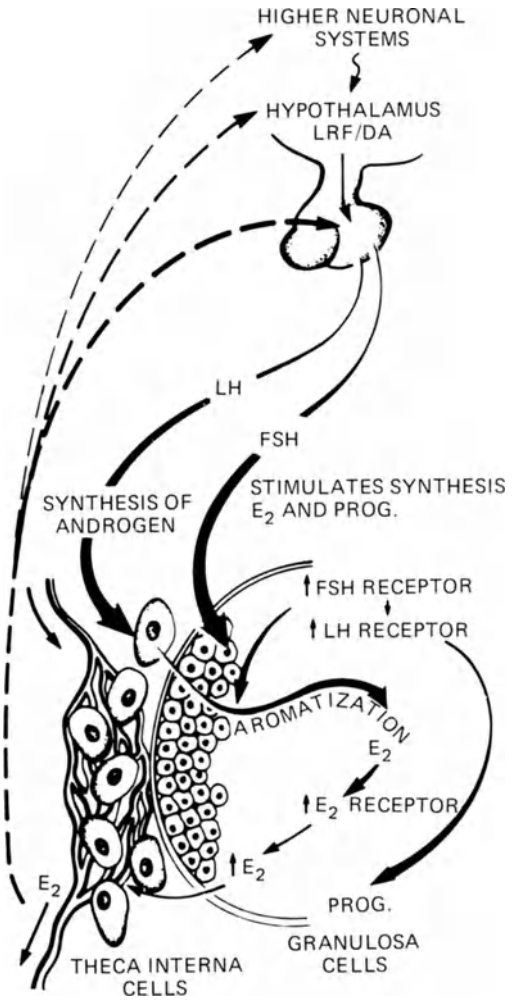

Figure 7-3. Gonadotropin-ovarian interaction in the regulation of follicular maturation and steroidogenesis. From Yen SSC, Jaffee RB: The human menstrual cycle. In Yen SSC, Jaffee RB (eds): Reproductive Endocrinology: Physiology, Pathophysiology and Clinical Management. Copyright 1978 by W.B. Saunders Co., Philadelphia. Reproduced with permission.

Excessive Ovarian Androgen Production in PCOS

An essential feature of PCOS is increased ovarian production of androgens.[32–34] The major androgens produced in excess are

Figure 7-4. Granulosa and theca lining in polycystic ovarian syndrome. From Givens JR, et al: Familial ovarian hyperthecosis: a study of two families. American Journal of Obstetrics and Gynecology 110:964, 1971. Reproduced with permission.

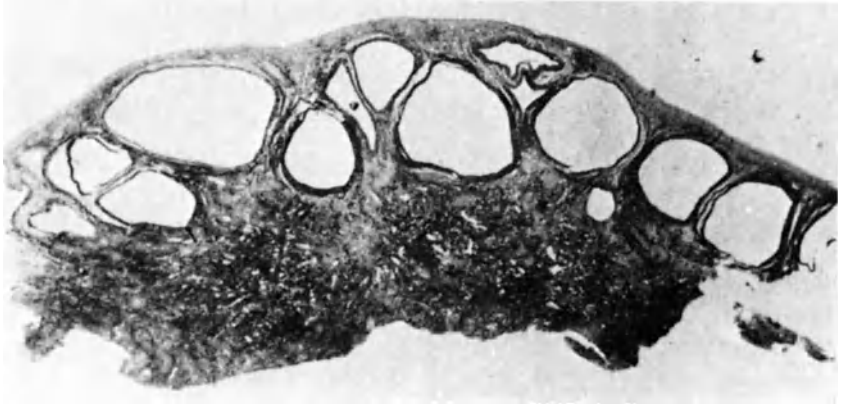

Figure 7-5. Subcapsular cyst and early antrum formation in polycystic ovarian syndrome. Reproduced with permission from Givens JR: Polycystic ovarian disease. In Givens JR (ed): Gynecologic Endocrinology. Copyright © 1977 by Year Book Medical Publishers, Inc., Chicago.

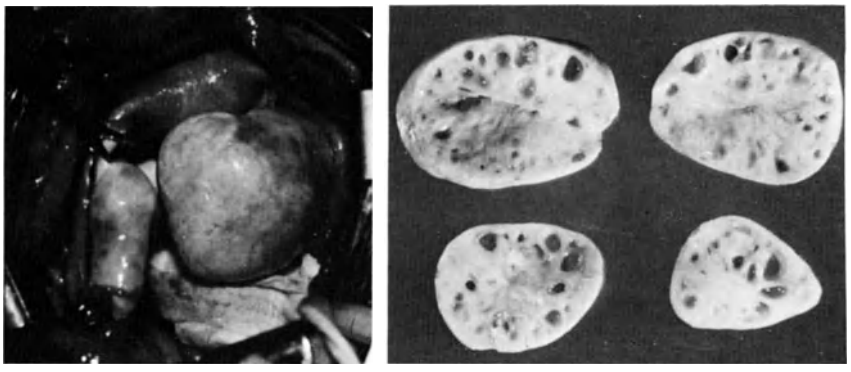

Figure 7-6. Gross features of polycystic ovaries. From Givens JR: Hyperandrogenism: diagnosis and therapy. Research Resources Reporter 8:3, 1984 (a publication of the U.S. Dept. of Health and Human Services). Courtesy of J.R. Givens.

androstenedione, testosterone, and dehydroepiandrosterone—the same ones produced by the normal ovary. Therefore, the androgen abnormality differs from normal quantitatively, not qualitatively.[32,33] The hormonal derangement in PCOS is most likely a reflection of the steroidogenic capabilities and limitations of the cells involved.[35] The abnormally high ratio of androgens to estrogens is both a reflection of thecal cell and stromal dominance and the relative deficiency of granulosa cell function.

Adrenal Hyperandrogenism and PCOS

Broster observed that women with adrenogenital syndrome had enlarged and polycystic ovaries with diffuse thickening of the tunica.[36] This finding, however, has not been universal. While others have reported an association between the two disorders,[37-41] Blackman[42] and Jones[43] did not find classic PCOS in 17 cases of adrenogenital syndrome, although two had some degree of perifollicular luteinization. The ovaries of women with Cushing's syndrome do not exhibit classic findings of PCOS because of the absence of cortical stromal hyperplasia, thecal luteinization, and surface fibrosis.[44] Enlarged polycystic ovaries also are seen in the late onset or attenuated form of 21-hydroxylase deficiency.[45] PCOS may be related in some way to both the degree of adrenal androgen excess and the time of its appearance. The enzymatic deficiency may be so mild that it is not evident when androgens are sampled under basal conditions, yet the characteristic hallmarks of 21-hydroxylase deficiency are present with ACTH stimulation. Enlarged polycystic ovaries have been reported in patients with classical and late onset 11-β-hydroxylase deficiency.[46,47] Androstenedione, however, competitively inhibits 11-β-hydroxylase activity.[48] Excessive androstenedione production and polycystic ovaries may influence 11-β-hydroxylase activity secondarily in the adrenal cortex.

Another cause of late onset congenital adrenal hyperplasia and polycystic ovaries is a deficiency of 3-β-hydroxysteroid dehydrogenase Δ_{4-5} isomerase activity that is necessary for the conversion of Δ_5 to Δ_4 steroids in both the adrenal cortex and ovaries.[49]

Hyperresponsiveness of urinary 17-ketosteroids to ACTH with no evidence of any enzymatic block was found in some patients with PCOS before more specific assays were available.[50] Subsequently, hyperresponsiveness of adrenal androstenedione to ACTH has been noted in hirsute women, many of whom had enlarged polycystic ovaries.[51-54]

Polycystic ovaries also have been associated with a virilizing adrenal adenoma.[55]

We and many others have noted the frequency of involvement of adrenal androgen secretion in PCOS, independent of any demonstrable classic adrenal enzyme deficiency or tumor.

Obesity and Polycystic Ovary Syndrome

Polycystic ovaries and anovulation may be associated with simple obesity.[56] An increased LH-to-FSH ratio in moderately obese women similar to that of PCOS has been reported.[57]

In a large heterogeneous group of patients suspected of having hyperandrogenism, plasma total testosterone (T) and free testosterone levels correlated positively with body weight.[58] A significant negative correlation also was noted between body weight and sex hormone binding globulin (SHBG) as measured by the binding capacity. Weight was positively correlated with T despite a negative correlation between weight and SHBG.[58] There is a high incidence of obesity among hyperandrogenic females, and animal studies have demonstrated that T treatment increases body weight.[59] Hyperinsulinemia and the decreased binding capacity of plasma for testosterone and estradiol are mechanisms by which obesity could cause derangement of follicular maturation and/or atresia. Weight reduction corrects oligoanovulation and the increased LH-to-FSH ratio.

Central Nervous System Disorders and PCOS

Polycystic ovaries have been associated with destructive lesions of the central nervous sys-

tem. Bartuska et al[60] documented a history of CNS injury in five patients with bilateral polycystic ovaries. An 18-year-old female had postencephalitis Parkinson's disease with diffuse injury of the basal ganglia, hypothalamus, and adjacent area. This is particularly interesting in view of the increased sensitivity of LH secretion to the suppressive effect of dopamine in women with PCOS.[61] Decreased dopaminergic inhibition in the hypothalamus is implied in at least some women with PCOS.

Excessive prolactin secretion occurs in approximately 30% of females with PCOS. Hyperprolactinemia may be due to a pituitary tumor or functional derangement of the control mechanism for prolactin secretion.[62,63] Thus the elevated prolactin levels in association with polycystic ovarian disease may be primary or secondary. Acromegaly with excessive growth hormone is associated with lowered SHBG levels,[64] and elevated free testosterone can be associated with polycystic ovaries.

PCOS Associated with Acanthosis Nigricans and Hyperinsulinemia

Four types of presentation have been reported for this syndrome: ovarian tumor and PCOS;[65] PCOS without ovarian tumor;[66] pineal gland hyperplasia, diabetes, and virilism;[67,68] and congenital lipodystrophy with diabetes.[69] These four syndromes link acanthosis nigricans, insulin resistance, and hyperinsulinemia to PCOS (Fig. 7-7). This is of special interest because of the recent documentation that insulin potentiates the stimulatory effect of LH on the secretion of androstenedione by theca cells.[30] Whether this later finding is pharmacologic or has physiologic relevance remains to be determined.

Health Consequences of PCOS

If the androgen dynamics in PCOS are an abnormality of quantitative rather than qualitative androgen production, what are the ill effects? Hyperandrogenism has been correlated with hyperinsulinism[70,71] independent of the known correlation between obesity and hyperinsulinism. The obese hyperandrogenic female is likely to display hyperinsulinemia. Some suggest that androgen levels correlate with the lipid profile of cardiovascular risk.[72,73] Hyperestrogenism associated with hyperandrogenism and anovulation forms the basis for Korenman's estrogen window hypothesis.[74] (see Chapter 14) Anovulation may be a potential etiology in the endocrine background conducive to breast carcinoma. Prolonged anovulation with hyperandrogenism frequently is associated with hyperestrogenism and an endocrine background that promotes endometrial carcinoma. The most frequent endocrine history for the development of endometrial carcinoma in women under 40 is PCOS. The youngest patient with endometrial cancer that the author has diagnosed was 19, obese, anovulatory, and hirsute. The

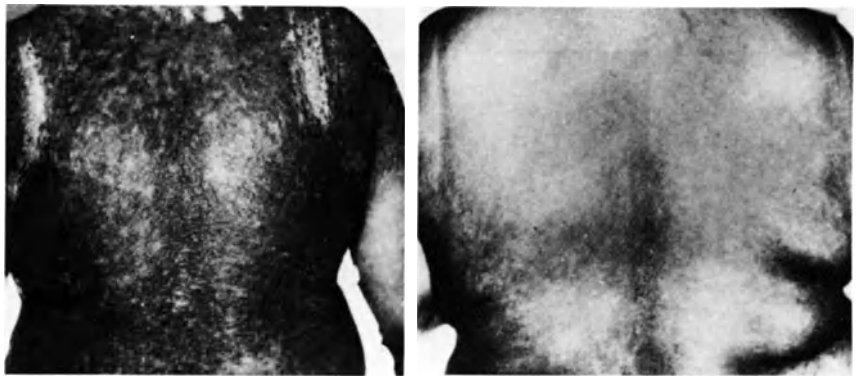

Figure 7-7. Acanthosis, insulin-resistance, and hyperinsulinemia in polycystic ovarian syndrome. From Givens JR, et al: Remission of acanthosis nigricans associated with polycystic ovarian disease and a stromal luteoma. J Endocrinol Metab 38:352, 1974. Copyright © 1974, The Williams & Wilkins Co., Baltimore. Reproduced with permission.

Table 7-1. Plasma Total and Free Androgen Concentrations during Female Adolescence.

Stage	n	Testosterone		TEBG (nM)	DHAS (μg/dl)
		Total (ng/dl)	Free (pg/ml)		
I. Prepubertal (10–11.8 yr)	16	17 ± 5 (9–26)[a]	3.8 ± 1.1 (2–6)	29 ± 14 (2–54)	68 ± 42 (11–150)
II. Early puberty (10.3–12.7 yr)	24	21 ± 10 (9–42)	4.8 ± 2.8 (2–11)	30 ± 15 (9–60)	93 ± 62 (22–240)
III. Midpuberty (10.4–15.0 yr)	20	34 ± 13 (16–59)	7.5 ± 3.1[b] (3–14)	30 ± 9 (14–48)	97 ± 46 (31–190)
IV. Postmenarcheal (11.4–15.6 yr)	26	40 ± 9[b] (24–55)	8.8 ± 2.3[b] (5–13)	28 ± 6 (19–40)	170 ± 100[b] (51–390)
Adult follicular phase (18–25 yr)	21	49 ± 18[b] (23–86)	7.4 ± 2.6[b] (4–12)	40 ± 15 (12–63)	170 ± 80[b] (61–400)

Values are mean ± SD.
[a]Normalized 90% population limits.
[b]Significantly different ($P_2 < 0.05$) from stage II.
Reproduced with permission from Moll GW Jr: Plasma free testosterone in the diagnosis of adolescent polycystic ovary syndrome. Journal of Pediatrics 102:462, 1983.

metabolic consequences of abnormal androgen dynamics are likely to be substantial.

A problem of critical importance to the adolescent is facial hirsutism and/or acne. It is now recognized that acne is formed on a background of increased androgenic activity.[75] Facial hirsutism can be disfiguring and should not be taken lightly because of its potential effects on the developing personality.

How Should One Evaluate the Adolescent with Signs and Symptoms of Hyperandrogenism?

Girls usually have female adult levels of free testerone by the time they achieve Tanner stage 3 of breast development (Chapter 8) and within the year before menarche (Table 7-1).

In an evaluation of 138 patients suspected of having hyperandrogenism, we found elevated free testosterone in 82%. This was the most frequently elevated parameter.[57] Dehydroepiandrosterone sulfate (DHEA-S) was elevated in 59%, and 93% had hyperandrogenism on the basis of free T and DHEA-S levels (Fig. 7-8).[57] Serum total testosterone and DHEA-S determinations are a useful screening test to rule out a tumorous source of hyperandrogenism. Total testosterone greater than 200 ng/dl or DHEA-S greater than 700 μg/dl requires more complete evaluation to rule out an adrenal or ovarian tumor.

Dexamethasone suppression and/or ACTH stimulation studies may be helpful as an adjunct in selected cases. Three-α-androstenedione glucuronide may prove a useful reflection of peripheral androgenicity.[76] Recent years have brought to the forefront the idea

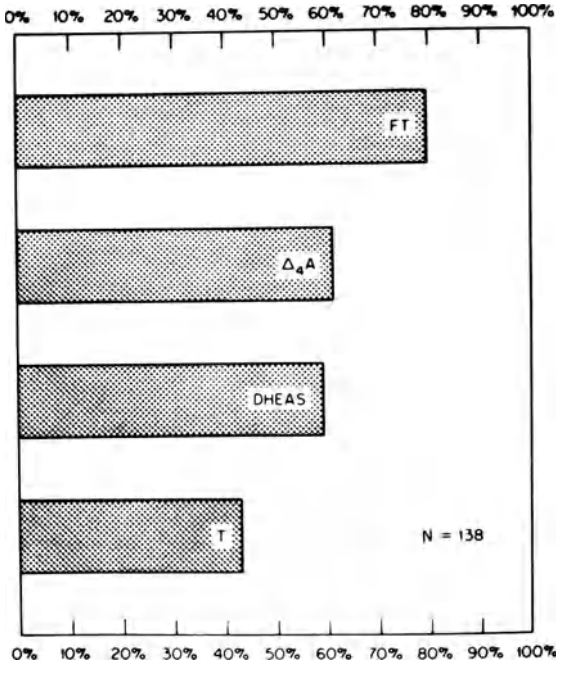

Figure 7-8. Frequency of elevation of each of the androgens in 138 women suspected of having hyperandrogenism. From Wild RA, et al: Androgen parameters and their correlation with body weight in 138 women thought to have hyperandrogenism. American Journal of Obstetrics and Gynecology 146:604, 1983. Reproduced with permission.

that the skin is a significant endocrine organ. Androgen receptors and estrogen receptors are present. Local growth factors are being recognized as playing a significant role in hirsutism even in cases where hyperandrogenism cannot be documented. Androgens can induce 5-α-reductase activity in an amplification effect.[77] Thus, relatively weak androgens can be converted to more potent androgens following androgen exposure. Salivary testosterone correlates well with free testosterone in plasma[78] and appears a useful and increasingly available determination in the adolescent.

Treatment of Hyperandrogenism in the Adolescent

The first task when encountering PCOS is to identify and treat any underlying endocrinopathy. Obesity is best handled through a team approach that uses a nutritionist who is sensitive to the emotional needs of the adolescent. Weight reduction can in and of itself contribute to reversing the abnormal endocrine dynamics seen in patients with PCOS.

If cystic acne is the main concern, isotretinoin, a synthetic vitamin A analog, may be used in its treatment.[79] If birth control is required, suppression of hyperandrogenism is noted at multiple sites. Oral contraceptives (35 μg preparations) increase SHBG, diminish free testosterone, and suppress LH-dependent hyperandrogenism.[80] They not only suppress the ovarian component to hyperandrogenism, but also suppress the adrenal component to androgen excess in hirsute patients.[53] This finding has recently been confirmed[54] and has significant practical application in the treatment of the hirsute patient. Low dose oral contraceptives have been shown to diminish free testosterone levels.[81] Spironolactone (100–200 mg daily) can be used to diminish hirsutism.[82] Although cost may be a factor, it is now known that the drug has a longer half-life than originally suspected. One-time administration of increasingly smaller doses has proven effective. When given cyclically and discontinued with menses, surprisingly high continuation rates have been noted. Because ovulation frequently is not inhibited, the possibility of pregnancy should be discussed. Cyproterone acetate with ethinyl estradiol has been effectively studied and widely used in Europe. The likelihood of wide usage and acceptance in the United States, however, seems minimal in light of the FDA's concern about progestin-associated teratogenicity and carcinogenesis.

For these women with documented congenital adrenal hyperplasia, or a significant adrenal component to their androgen excess, glucocorticoid suppression (dexamethasone 0.5 mg po qod), at physiologic to subphysiologic levels, has been helpful. Long-acting glucocorticoids can have profound adrenal gland suppression. The individual's metabolism of dexamethasone must be monitored. If cortisol levels are maintained greater than 2 μg/dl on alternate day morning assays, significant long-term problems with prolonged adrenal suppression are unlikely.[83]

Summary

Problems of hyperandrogenism are becoming increasingly recognized in the adolescent female. Manifestations of androgen excess can have both far-reaching metabolic implications and significant effects on body image. At a crucial time in personality development, these problems should not be taken lightly. A common pathophysiology associated with androgen excess is the polycystic ovary syndrome. Awareness of this fascinating syndrome and its metabolic implications can alert health care professionals so that the adolescent's metabolic, physical, and psychologic needs are best addressed. Individualization of treatment is the rule. Team approaches to the diagnosis and treatment of the disorder have proven effective in reversing the pathophysiology that has led to hyperandrogenism.

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Breast Disorders 8

John Pietsch

Many of the problems brought to the attention of the physician concerning the adolescent breast involve variations of normal development that are accentuated by varying degrees of emotional and social overlay. Although they may appear minor to the physician, these problems are often quite real and distressing to the patient.[1] Less common are true congenital or acquired abnormalities of the breast, some of which require surgical attention. Although few of these problems are life threatening, they are of great importance to the patient and deserve proper consideration and management. Knowledge of both the variations of normal breast development and congenital and acquired disorders is essential for proper management of these young people. Partly as a consequence of the importance society has placed on breast development, disorders of this organ in the adolescent are of great importance to their self-image and sexuality. In addition, there is often a fear of being different or less attractive than one's peers. Thus emotional support as well as appropriate surgical, endocrinologic, or psychiatric consultation is necessary for optimal care for each individual patient.

Embryology

Beginning around the sixth week of fetal development, epidermal cells migrate into the underlying mesenchyme forming the primitive mammary ridges or "milk lines." This thickening of the ectoderm extends from the axilla to the groin. By the tenth week, atrophy of the upper and lower portions of the ridges occurs, leaving the pectoral area to develop secondary buds, lactiferous ducts, and mammary glands. Later, the developing breast is augmented by growth of the surrounding mesenchyme which provides fibrous connective tissue and fat.

Normal Development

In childhood, the breast is confined to the area beneath the areola. It is made up of epithelium lined ducts surrounded by connective tissues. This fact is critical in the management of real or suspected lesions of the prepubescent breast. An injudicious biopsy may well destroy a substantial portion of breast tissue. With the onset of puberty, increasing amounts of hormones are released by the hypothalamus, pituitary, ovaries, and adrenal glands; the result is breast development. In addition to the well-recognized effects of estradiol, prolactin, and progesterone, breast development is also dependent upon the interactions of testosterone, cortisol, insulin, thyroid, and growth hormones.[2,3] Thelarche (breast development) is frequently the first clear-cut sign of the onset of puberty.

There is considerable variation in the timing of the onset of puberty. Breast development occurs in most girls between years 8.5 and 13.[4] Failure of initiation of breast development by age 14 is generally considered to be abnormal and a cause should be sought. The rate of breast growth also varies. Some girls pass from stage 1 to stage 5 in only 2 to 3 years, whereas

Table 8-1. Marshall-Tanner Classification of Breast Development.[4]

Stage 1	Preadolescent; elevation of papilla only
Stage 2	Breast bud stage; elevation of breast and papilla as a small mound; enlargement of areolar diameter
Stage 3	Further enlargement of breast and areola, with no separation of their contours
Stage 4	Projection of areola and papilla to form a secondary mound above the level of the breast
Stage 5	Mature stage; projection of papilla only, due to recession of the areola into the general contour of the breast

others may take until the early 20s for complete breast development (Table 8-1).

Both of these factors should be taken into consideration in counseling a developing adolescent. As described subsequently, what may appear to be abnormal early in development may become normal with time. Four-and-one-half years may be required for the completion of the pubertal process, i.e., the onset of menarche. This information must be taken into account in decisions regarding the evaluation of abnormal pubertal development. An integral part of the physical examination in this age group includes careful assessment of the breast and an attempt to elicit any nipple discharge. The formation of breast tissue is integral to both the physical and the psychologic development of the female. Thus, when breast abnormalities occur, health care providers must address the psychologic as well as the physical aspects. Early surgical intervention in cases of abnormal breast development is also ill-advised and may require later revision due to ongoing growth of the adolescent breasts.

Congenital Anomalies

Congenital absence of a breast (amastia) is quite rare. If present, it is usually unilateral and often associated with other abnormalities such as found in Poland's syndrome (aplasia of the pectoralis muscles, rib deformities, webbed fingers, and radial nerve aplasia). Absence of a breast is much more likely to be secondary to iatrogenic causes as discussed later. Surgical reconstruction in amastia varies in complexity depending upon the degree of chest wall and muscle abnormalities.[5] Absence of a nipple (athelia) is likewise rare and may or may not be associated with absent breast tissue.[6] Treatment of congenital anomalies usually requires surgical correction.

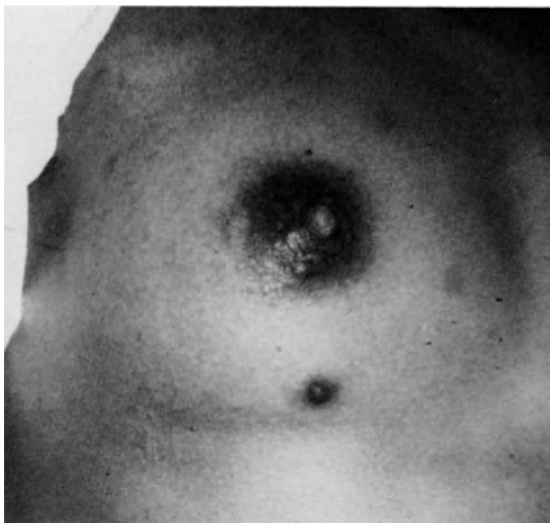

Figure 8-1. Supernumerary nipples in a 21-year-old female.

Supernumerary breasts (polymastia) or supernumerary nipples (polythelia) are relatively common (Figs. 8-1 and 8-2). These occur along the "milk lines" and are usually asymptomatic. Polythelia is found in approximately 2% of the population while polymastia is less common. Both entities may be familial. There appears to be an association between polythelia and anomalies of the urinary and cardiovascular systems.[7] This additional tissue

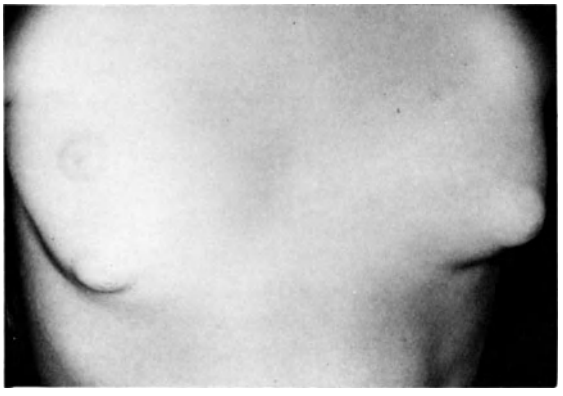

Figure 8-2. Supernumerary nipple closely attached to the superior outer quadrant of the right breast in a 15-year-old female.

is rarely functional, but accessory breasts and nipples are, in theory, subject to the same physiologic and pathologic changes as the normal breast.[8] Surgical excision of accessory breasts or nipples is usually not necessary. However, if these structures should become symptomatic, i.e., an axillary breast, or cosmetically important, removal can be easily performed. If the accessory breast tissue does not have an accompanying nipple, diagnosis of this mass lesion may be difficult. It is important to differentiate this condition from hidradenitis suppurativa. Its location in the "milk line" may be a useful sign, but often excisional biopsy is necessary to clarify the diagnosis.

Breast Abnormalities

Asymmetry

A difference in size between the developing breasts is common during early adolescence (Fig. 8-3). These differences usually decrease as development progresses and are barely noticeable by the time development is complete. Reassurance is often all that is necessary; but should the asymmetry persist, either unilateral breast reduction or augmentation may be indicated after completion of breast growth. Early surgical intervention is not recommended since further breast growth may either make the procedure unnecessary or require revision.

Hypoplasia

Hypoplasia of the breast varies in degree from near complete absence of breast tissue to well-formed breasts considered by the patient or others to be "too small" (Fig. 8-4 and 8-5). There are three general causes of poor or absent breast development. Some girls simply have delayed onset and slow breast development but are otherwise normal. There may be a family history of late development which helps in both diagnosis and in reassuring these patients. Others with normal breast tissue have disorders causing failure or suppression of ovarian function. These patients usually have primary amenorrhea and poorly developed secondary sexual characteristics. Diagnosis and treatment of the underlying disorder, as discussed elsewhere, will often stimulate breast development. These disorders include chromosomal abnormalities, androgen producing tumors, gonadal dysgenesis, and adrenal hyperplasia. A third and less well-

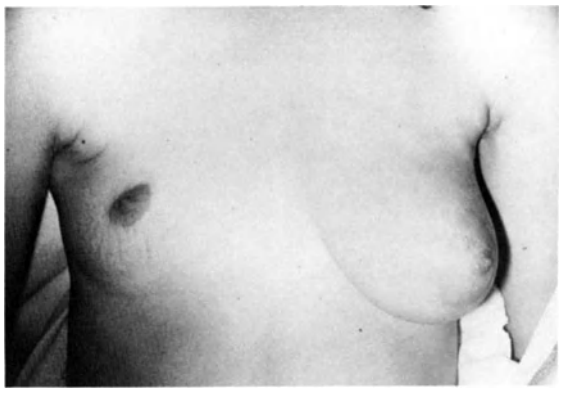

Figure 8-3. Asymmetric breast development in a 19-year-old female.

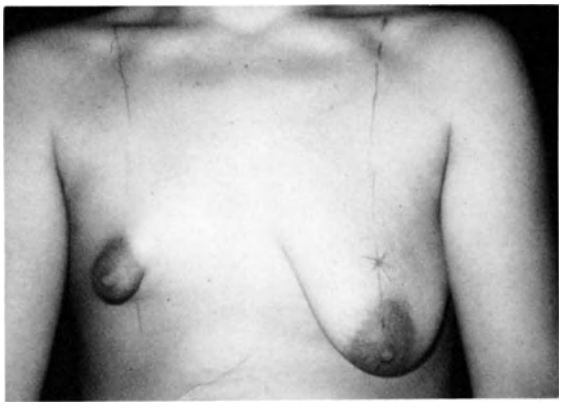

Figure 8-4. Nineteen-year-old female with asymmetric breast development: right hypoplasia and left ptosis.

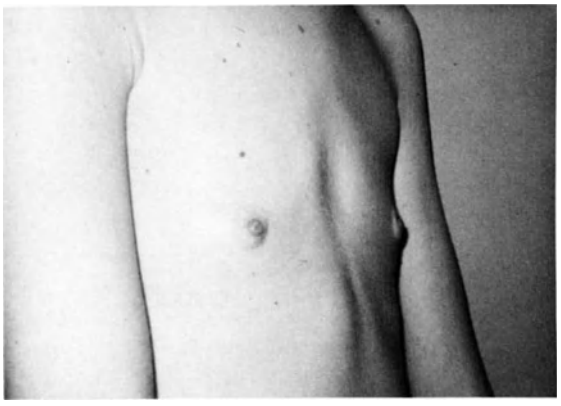

Figure 8-5. Hypoplasia of the breast in a 19-year-old female.

defined group includes those in which hypoplasia seems to be secondary to a partial failure of end-organ response. These breasts are small, but have normal sensation and function. In response to pregnancy, they enlarge and often produce milk for the infant. Following cessation of lactation, the breasts return to their prepregnancy state.

Because of the large emotional and self-image component to the problem of idiopathic breast hypoplasia, simple reassurance may not be adequate. The emphasis on the female breast by the entertainment and advertising industries has perpetrated the concept that happiness and sexual fulfillment are dependent upon "socially acceptable" breast development. There may be pressure from the adolescent and her family for surgical intervention. It may be helpful to the young person to speak with older women who have achieved these goals without the need for surgical intervention. If augmentation mammoplasty is recommended, it should be delayed—if possible—until breast development is complete. One measure of this end point is the lack of measurable breast growth over a 6-month interval in the late adolescent.[9] Generally, augmentation will not interfere with lactation, and breast feeding is possible.

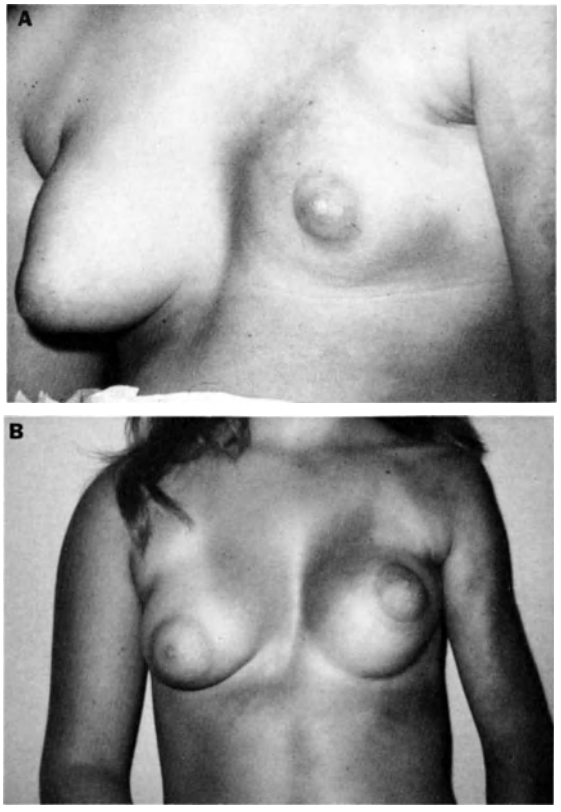

Figure 8-6. A Thirteen-year-old female with scleroderma of the left breast. **B** After breast reconstructive surgery.

Atrophy

Breast atrophy is occasionally seen in adolescents and is almost uniformly secondary to dietary changes. Reduction in protein intake either from a "crash diet" or anorexia nervosa results in the loss of subcutaneous tissue and an apparent weakening of the fibrous supporting tissue. This atrophy can be reversed with adequate nutritional support. If dieting is desirable, a balanced intake of nutrients is essential to the health of the developing adolescent. Thickening of the skin caused by swelling and thickening of fibrous tissue with eventual atrophy of the epidermis of the breast (scleroderma) may be considered with breast atrophy (Fig. 8-6). Treatment of breast atrophy secondary to scleroderma may require surgical intervention.

Hypertrophy

Massive breast enlargement (macromastia) which occurs during puberty and early adolescence is called virginal hypertrophy (Fig. 8-7) to distinguish it from hypertrophy of pregnancy. The etiology is unknown, but unsuspected pregnancy must be ruled out as the cause of the hypertrophy. Hormonal imbalance is thought to be a major etiologic factor. Virginal hypertrophy occurs over a relatively

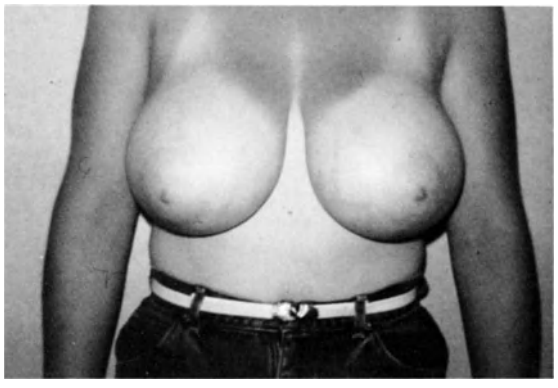

Figure 8-7. Virginal hypertrophy in a 17-year-old female.

brief period of time and is usually bilateral. A giant fibroadenoma may be mistaken for unilateral hypertrophy. Girls between 13 and 17 are most commonly affected. Breast hypertrophy poses both physical and psychologic problems for the adolescent. The size and weight of the breasts often cause posture problems in addition to discomfort. More troublesome, however, are the changes in self-image and the social consequences of extremely large breasts in a young girl. Treatment is reduction mammoplasty, but must be accompanied by strong emotional support since a delay in surgery is often indicated. Ideally, the operation should be delayed until late adolescence to allow for complete breast development, especially in cases of marked asymmetry, but this may be difficult because of pressure from the adolescent and her family. They should be made aware of the fact that, although the cosmetic results of reduction mammoplasty are often quite good, the extensive tissue resection and relocation of the nipple may result in decreased sensation and altered lactation. In general, breast feeding is not recommended in these patients. Successful treatment requires a close working relationship between physician, surgeon, patient, and her family. A possible alternative to surgical correction is medical treatment with danazol (Danocrine), an isoxazole derivative of testosterone.[10,11]

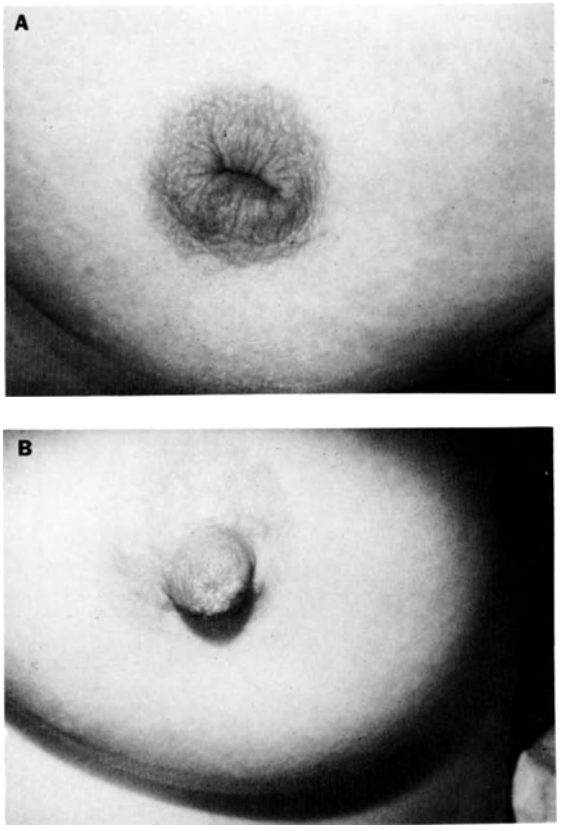

Figure 8-8. Twenty-year-old female with inverted nipple preoperatively (**A**) and postoperatively (**B**).

Inverted Nipples

Upon completion of breast development, inverted nipples are occasionally seen. This condition may pose a cosmetic problem for the late adolescent. Therapy requires surgical correction. The patient must understand, however, that the probability of successful breast feeding is virtually nil once surgical correction is performed for this problem (Fig. 8-8).

Neonatal Breast Abnormalities

The neonate in the first 2 weeks may have bilateral breast hypertrophy secondary to the elevated circulating endogenous steroid hormones of late gestation. This condition is self-limited and requires observation only.[12] In addition, breast milk, known as "witch's milk," may be elicited from the nipple. It may be exacerbated by repeated manipulation of the breasts. Occasionally, mastitis may develop. This is generally due to staphylococcus and will respond to parenteral antibiotics and manual expression of purulent material.

Premature Thelarche

Premature thelarche sometimes may occur in a pediatric patient. It is characterized by bilateral breast development before 8.5 years. It is not accompanied by other signs of pubertal development. No treatment other than observation is required.[13] This condition is most likely the result of an increase in end organ sensitivity to estrogen produced by luteinized or cystic ovarian follicles. Premature

breast development also may be a symptom of precocious puberty (see Chapter 14).

Mastodynia

Painful breast engorgement (mastodynia) may occur at puberty. It frequently has a cyclic pattern; analgesics, nonsteroidal antiinflammatory drugs such as naproxen sodium (Anaprox) and ibuprofen (Motrin), as well as supporting brassieres often are helpful in alleviating discomfort. For the adolescent of adult height and weight, α-tocopherol (vitamin E) in doses of 600 IU daily is beneficial.

Galactorrhea

The spontaneous flow of milk from the nipples is called galactorrhea. The evaluation of this condition is the same for adolescents and adults. Assessment consists of determining a serum prolactin level, preferably in the early morning and ideally not immediately after examination[14] or meals.[15] If prolactin is elevated, a serum thyroid stimulating hormone (TSH) should be obtained to rule out primary hypothyroidism and increased prolactin secondary to an increase in thyroid releasing hormone (TRH), which stimulates both TSH and prolactin release. Serum prolactin levels greater than 100 ng/ml should necessitate computerized tomographic scanning of the sella turcica to provide detailed assessment of the pituitary gland; diagnosis of microadenomas (less than 10 mm in diameter) or macroadenomas (greater than 10 mm), with or without suprasellar extension, may be determined. If the prolactin level is less than 100 and the TSH normal, a coned-down view of the sella turcica may be obtained to rule out a pituitary tumor greater than 13 mm. Treatment of galactorrhea depends upon the etiology and the desires of the patient. Does she, for example, want to become pregnant? If the prolactin level is normal and the patient has no spontaneous galactorrhea, observation is the treatment, with serum prolactins every 6 months and a yearly coned-down view of the sella turcica. Further assessment may be indicated if a pituitary tumor is found. Treatment may consist of observation, medical therapy with bromocriptine mesylate (Parlodel), surgery, or radiation therapy.

Trauma and Inflammation

Breast trauma in adolescent females, while uncommon, is increasing because of more frequent participation in contact sports. Usually these sports injuries result in a local contusion or hematoma which resolves without incident. Occasionally fat necrosis occurs, resulting in either late cystic changes in the breast or fibrosis with retraction of the skin or nipple over the injured area. These late changes may mimic those found with malignancy.[16] A biopsy may be necessary to differentiate the two in the older adolescent or young adult.

Even more deforming are burns to the chest wall in children and adolescents. Most burns do not destroy the glandular tissue of the breast, but the subsequent scarring and contraction of the skin can lead to marked deformity of the developing breast. Generally speaking, the younger the patient and the deeper the burn, the more severe the ultimate deformity. Staged scar releases with skin grafting as breast development progresses may lessen the deformity, but formal breast reconstruction may be necessary once development is complete.[17]

Iatrogenic trauma, usually the result of ill-advised biopsy or excision of breast tissue, is an especially catastrophic and worrisome problem.[18] The scenario is one of an 8- or 9-year-old girl in whom the mother has found a "lump" under one nipple. This discovery is followed by interpretation of the "lump" as disease by an inexperienced surgeon. An incisional or excisional biopsy of the normal breast bud is then performed. Because of the resulting loss of breast tissue, there is a marked deformity in the breast as normal development occurs. Breast biopsies in the prepubertal child are rarely indicated and should only be performed after appropriate consideration and consultation.

Mastitis and Abscess

Both mastitis and breast abscess require appropriate antibiotic therapy. The spectrum of antibiotic coverage should include staphylococcus, streptococcus, and *Escherichia coli*. Incision and drainage may be necessary. On occasion, *Pseudomonas* may be cultured, and

appropriate antibiotic therapy must be administered.

Mammary Dysplasia (Chronic Cystic Mastitis)

Mammary dysplasia is a diagnosis found by examination. It is a common lesion in the female breast, characterized by changes associated with the normal menstrual cycle. The etiology may be related to "hormonal imbalance," possibly a relative excess of estrogen and deficient corpus luteum activity. This produces exaggerated responses in the breast tissue. It is especially common in the upper outer quadrants of the breast and is associated with premenstrual pain and tenderness. Anovulatory cycles also can produce these symptoms.[19] Mammography often is helpful in establishing the diagnosis. Treatment depends upon the degree of symptomatology. Danazol therapy in daily doses of 100–800 mg is frequently beneficial.[20] Avoiding methylxanthines (coffee, tea, cola), chocolate, and dairy products also may help.[21] Brassieres that offer firm support may ease the discomfort.

Tumors

Breast tumors in the prepubertal girl occur very infrequently. Although more common in adolescence,[22–25] the probability of malignancy is low.[26,27] However, Gogas et al found in a series of 63 breast masses in adolescents one angiosarcoma, one lobular carcinoma, and one lymphosarcoma.[27]

The most common neoplasm of the adolescent breast is the fibroadenoma. These vary in size from a small, firm nodule to a large mass which may have quite rapid growth and is usually painful. Most fibroadenomas are firm, mobile, solitary lesions, but may be multiple in approximately 20% of patients. These tumors appear to be hormonally dependent as evidenced by the fact that they may become larger or smaller during the menstrual cycle or with exogenous estrogens. Treatment of a fibroadenoma is excisional biopsy, but unless the mass is quite large or painful there need be no rush in removing it. Often a period of observation extending through several menstrual cycles is helpful in distinguishing small fibroadenomas from so-called adolescent mastopathy which spontaneously resolves.

Solitary or multiple cysts of the adolescent breast are uncommon. They are usually associated with antecedent fat necrosis or ductal ectasia and not with fibrocystic disease of the breast. The diagnosis of breast cysts is made by needle aspiration. If the cyst fluid is clear and does not recur, no further treatment is necessary. However, if the fluid is bloody or the cyst recurs, the possibility of malignancy increases and excision of the cyst is indicated.

Cystosarcoma phylloides is an uncommon breast tumor of adults which has been reported to occur in adolescents.[28] It is characterized by asymmetric breast enlargement with a firm, mobile circumscribed mass. The overlying skin may be stretched and shiny with distended veins. It is the second most common cause of massive breast enlargement in the adolescent age group.[29] The tumors frequently rapidly enlarge and can become quite sizeable. Fixation of the tumor to the skin or chest wall is rare. The majority of these tumors are benign, but malignant cystosarcoma phylloides with eventual metastases has been reported.[30] Since local recurrence of cystosarcoma phylloides often occurs following simple removal, excision of the mass plus a margin of normal tissue is recommended. If malignancy is noted, a simple mastectomy is the preferred treatment.[31]

Other more uncommon tumors may occur in the adolescent breast. Most of these, including intraductal papillomas and neurofibromas, are benign.

Fat necrosis presents as a firm, hard lump that is often tender but rarely enlarges after it is first diagnosed. It is frequently associated with trauma. The problem lies in differentiating it from carcinoma. Skin retraction, irregular edges, and fine stippled calcification may be found by mammography.[16] Treatment of choice is an excisional biopsy.

Hamartoma is a mass that resembles a tumor but is assumed to represent the anomalous development of tissue natural to the breast rather than a true tumor. The presentation is similar to that of a fibroadenoma, and treatment is an excisional biopsy.

Malignant breast tumors are very rare in children and adolescents. Approximately 2% of breast cancers occur in women less than age

25. As in older women, a strong family history of breast carcinoma increases the risk, and these young women should be followed more closely. It usually presents as a unilateral, hard, tender mass that is slow growing. Diagnosis can be made by biopsy. In general, young females with breast carcinoma have an excellent prognosis.[32,33] Mastectomy, simple or radical, is the standard operative procedure. Due to the relatively small number of cases reported, lesser operations have uncertain benefit. Simple excision also has been reported as adequate therapy.[34]

Women who develop breast cancer and whose mothers had breast cancer do so 10 to 12 years earlier than women with negative family histories.[35] Familial breast carcinoma has been diagnosed in a 21-year-old female. Prophylactic mastectomy in a sibling should be considered if females in each generation of a family have had breast carcinoma. The use of adjuvant chemotherapy has not been well defined in this age group due to the small number of cases.[32,35]

Breast carcinoma may be related to exposure to unopposed estrogen. Korenman's estrogen window hypothesis[36] notes that during both early puberty and perimenopausal periods of a female's lifespan unopposed estrogen provides periods of maximal inducibility for breast environmental carcinogens. The latency period for breast cancer is 15 to 20 years, and may be initially associated with unopposed estrogen. In addition, anovulation has been associated with an increased incidence of breast carcinoma,[37] the hypothesis also being that unopposed estrogen produces breast neoplasms. Gambrel et al[38] have reported a protective effect when adding progestin therapy to exogenous estrogen treatment. While this specifically addressed postmenopausal women, it is logical that the addition of progestin therapy (e.g., in gonadal dysgenesis) may also prevent breast carcinoma in adolescents. Thus, administration of a progestin for 10 or more consecutive days should be prescribed with exogenous estrogen therapy.

Secondary malignancies of the breast are uncommon. Malignant lymphoma and acute leukemia may be associated with breast masses in adolescence.[39] In 2–3% of cases, Burkitt's lymphoma presents with breast masses. Usually, the breast involvement is part of the overall picture of the underlying leukemia or lymphoma and therefore should not be confused with a second disease process.

Summary

In treating adolescents with breast complaints or abnormalities, a conservative approach is often the most prudent. This must be accompanied by appropriate attention to the emotional and social consequences for the young person of both the problem and the proposed solution. Occasionally, surgical intervention may be indicated. The timing of this decision is often complicated by pressure from the patient and her parents. Evaluation and explanation of potential long-term developmental consequences vs. potential short-term benefits are necessary for proper decision making and optimal results.

Acknowledgment

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Surgical Emergencies in the Newborn 9

Thomas R. Weber and Jay L. Grosfeld

Many congenital anomalies can present as emergencies in the period immediately after birth. Prompt recognition and therapy frequently can mean the difference between life and death in these seriously ill neonates. Thus, it is important that physicians involved in childbirth have a thorough knowledge of these defects and their early management. It is the purpose of this chapter to both describe the various congenital anomalies that require surgical repair at or shortly after birth and to outline their appropriate early management. Frequently this means resuscitation and stabilization of the infant, with subsequent transport to a medical center where surgeons with special expertise can do the surgery, and the infant can receive the neonatal intensive care that is often critical for survival. It is rare that a newborn cannot be stabilized enough to allow transport to such a center. The recent dramatic improvement in survival for infants with many of these anomalies is mainly a result of advances in preoperative and postoperative care, which is best rendered at hospitals equipped to handle seriously ill neonates.

Esophageal Atresia and Tracheoesophageal Fistula

There are five variants of this anomaly (Fig. 9-1). The most common form is type C which occurs in 88% of cases. This includes a blind upper esophageal pouch and a tracheoesophageal fistula (TEF) that represents a direct route from the stomach to the tracheobronchial tree. This defect occurs in one in 1500 births, with males and females being equally affected. One-half of these infants are either premature or small for gestational age, while more than 70% have other anomalies. These additional factors make the management of these infants exacting and difficult.

Maternal hydramnios (greater than 1000–1500 cc amniotic fluid) can be an early clue to this defect. More than 90% of babies with esophageal atresia without a fistula (Fig. 9-1, types A and B) have hydramniotic mothers, whereas only 20% of pregnancies with types C and D defects result in hydramnios. In the latter cases, swallowed amniotic fluid spills over into the tracheobronchial tree, through the TEF, and into the gastrointestinal tract where it is normally absorbed.

Esophageal atresia (EA) should be suspected in any newborn who appears to have difficulty swallowing saliva and other liquids. This can occur at birth, or within several hours after

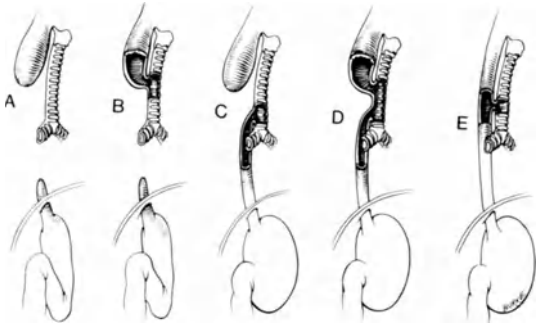

Figure 9-1. The five types of esophagal atresia and tracheoesophageal fistula. Type C is the most common form, comprising 88% of cases seen.

delivery. The babies frequently are seen "bubbling" at the mouth, which can quickly progress to coughing and gagging and may result in apneic or cyanotic spells. The source of the respiratory distress is twofold: First, secretions and saliva that cannot be swallowed spill over through the vocal cords causing upper respiratory obstruction. The ability of a newborn to clear his airway by coughing is limited, and frequent suctioning of these infants is necessary. Secondly, the TEF is a direct route for gastric acid secretions to enter the tracheobronchial tree. The consequences of gastric acid aspiration are well known, and the newborn lung is particularly susceptible to this type of severe injury. The risk of aspiration is increased by placing the baby in the supine position, as is routinely done shortly after birth, and by gastric distension caused by a flow of air from the trachea to the stomach through the TEF.

An immediate but gentle attempt at passing an orogastric tube with a soft radiopaque catheter should be done in any infant suspected of esophageal atresia. If there is resistance, a chest radiograph should be taken to assess the level of obstruction. Most cases of esophageal atresia can be diagnosed this way; an injection of contrast material is unnecessary and may be dangerous if it spills into the tracheobronchial tree. The radiographic detection of air in the gastrointestinal tract confirms a type C or D TEF, whereas an absence of air indicates a type A or B defect.

Once the diagnoses of EA and TEF are made, several simple maneuvers will decrease the possibility of severe respiratory distress. A small sump catheter (Replogle) should be positioned carefully in the upper esophageal pouch and put on gentle continuous suction. This will keep the airway clear. The child should be positioned so the head and chest are upright (such as in an infant seat), using gravity to keep gastric secretions within the stomach. An intravenous line should be established and broad-spectrum antibiotics administered (gentamicin and ampicillin). Oxygen should be given by mask as needed, while endotracheal intubation and positive pressure ventilation of the infant must be avoided unless absolutely necessary because much of the tidal volume will travel through the TEF into the baby's stomach and gastrointestinal tract. This may worsen the respiratory distress by elevating the diaphragm.

After the infant arrives at a tertiary care center, the placement of a gastrostomy tube under local anesthesia should be considered. This is a safe and efficacious procedure that keeps the stomach empty of secretions and air, thereby greatly reducing the chances of increasing respiratory distress from aspiration or an elevated diaphragm. Infants who are small for gestational age or premature or who have associated anomalies, sepsis, respiratory distress, or pneumonia should undergo careful evaluation, hydration, pulmonary toilet, and antibiotics prior to a thoracotomy to repair the defect. This delay usually lasts 1 to 4 days but should be as long as necessary to prepare the infant for this major operation. During this period catheter suction of the upper pouch is continued, the baby is kept upright, and the gastrostomy is maintained on gravity drainage. Intravenous hyperalimentation may be necessary if the delay is more than 2 or 3 days. A considerable reduction in operative mortality has occurred in recent series using this protocol.[1]

An extrapleural approach is used during the thoracotomy to avoid violating the pleural space should the anastomosis leak. The TEF is carefully divided and the opening in the trachea oversewn. The upper esophageal pouch is mobilized to or above the thoracic inlet to allow approximation of the ends of the esophagus. A one- or two-layer anastomosis is then done, usually with fine silk sutures. In the event the two ends cannot be approximated, there are several alternatives. If the gap is a centimeter or less, a circular myotomy through the muscle of the upper pouch but not into the lumen will gain a centimeter of length. If there is a larger gap the distal esophagus can be closed and the two ends brought as close together as possible. The area should be reexplored after spontaneous stretching, usually anywhere from 4 to 6 weeks. Other techniques such as electromagnetic or manual stretching of the proximal pouch over 6 to 8 weeks occasionally are successful in salvaging an esophagus. If the two ends cannot be approximated even then, a cervical esophagostomy should be done to enable the baby to swallow secretions. The infant is maintained on gastrostomy tube

feedings until 18 to 24 months, at which time an esophageal replacement is done with a segment of colon, stomach, or small bowel.

The results for primary repair of EA and TEF have improved markedly over the past 40 years, with survival rates of 85–90% in most large pediatric surgical centers. Many infants with associated anomalies require other surgery for these defects, which makes a careful follow-up mandatory.[2] Long-term problems of anastomotic stricture, gastroesophageal reflux, and abnormal esophageal motility require careful reevaluation and occasionally surgery.

Abdominal Wall Defects

Omphalocele

An omphalocele is a covered defect within the umbilical cord into which intraabdominal contents herniate.[3] The sac is composed of amnion externally and peritoneum internally and usually is intact unless ruptured during birth. This defect is associated with a greater than 50% incidence of associated anomalies and syndromes, including defects in the alimentary tract and genitourinary, musculoskeletal, cardiac, and nervous systems. It also is seen in infants with the Beckwith-Weidemann syndrome (gigantism, macroglossia, omphalocele, and hypoglycemia), trisomy 13-15 and 16-18, and exstrophy of the bladder or cloaca.

The size of the defect can vary from 1 to 2 cm to greater than 10 cm, and therapy depends upon the defect's size. The most immediate problems after birth are preserving body temperature, preventing excessive fluid loss and infection, and protecting the omphalocele sac and its contents. Thus, immediate coverage of the sac with moist sterile gauze is important. An intravenous line should be established and antibiotics (gentamicin and ampicillin) given. Unless the infant has aspirated gastric contents or meconium, endotracheal intubation usually is not required. An orogastric tube should be used and kept on intermittent suction to decrease the risk of aspiration.

When the defect is large and a large evaporative surface is exposed to the air, the baby's legs and abdomen (to the axillae) can be placed within a "bowel bag," a plastic bag with drawstrings that is available in most operating rooms. This effectively controls the loss of fluid and heat and allows safe transport to the pediatric surgery center.

The definitive therapy for the defect depends upon the condition of the infant, whether there are other anomalies, prematurity, and the size of the defect. Small omphaloceles in otherwise healthy infants usually can be closed primarily, whereas larger defects may require staged closure, which is accomplished by fashioning a Dacron-reinforced Silastic "silo" around the abdominal contents that cannot be reduced primarily. Over the ensuing 7 to 10 days the "silo" is squeezed gently from the top to gradually reduce the sac contents into the abdominal cavity, at which time the infant is returned to the operating room and the abdominal wall closed. Frequently, only skin coverage of the abdominal wall is possible, but this is satisfactory and allows secondary repair of the fascial defect when the infant is 12 to 24 months old.[4]

For infants with defects larger than 10 cm or those with other serious or life-threatening anomalies or trisomy syndromes, a nonoperative approach frequently is chosen. This consists of a twice-a-day application of an escharotic agent (0.5% silver nitrate), which will cause gradual epithelialization over the defect. Mercurichrome should be avoided because its use for this purpose has resulted in several cases of renal failure due to mercury poisoning.[5] Infants treated with silver nitrate should be kept in an infant warmer because of increased heat loss as a result of the wet dressing and carefully monitored for changes in serum sodium because of the hypotonic nature of the silver nitrate solution.

The overall mortality rate for infants with omphalocele approaches 35% in most series, with deaths resulting primarily from associated anomalies or trisomy syndromes.[6] Prematurity and giant defect also are adverse factors that must be considered in the management of these neonates.

Gastroschisis

Gastroschisis (belly cleft) is characterized by a full-thickness defect in the abdominal wall—usually to the right of the umbilicus—that results in extraabdominal evisceration of

intestine in utero.[7] Unlike omphalocele, the herniated gut is not covered, and the contact of the bowel wall with amniotic fluid (pH 7) results in a chemical (sterile) peritonitis. The eviscerated gut is thickened, edematous, and inflamed, and the bowel length is shortened. In addition, malrotation always is present. If the abdominal wall defect is small, the blood supply to some or all of the eviscerated bowel can be impaired causing bowel ischemia, frank necrosis, or intestinal atresia (10% of cases). However, usually the defect is sufficiently large to allow normal circulation to the bowel. The liver is virtually never part of the exposed viscera. In contrast to omphalocele the incidence of associated anomalies is very low. Forty percent of these infants are either premature or small for gestational age, which makes their management exacting and frequently complicated.

The immediate life-threatening problems that might occur after birth include hypothermia, hypovolemia due to loss of fluid from the exposed viscera, traumatic injury to the viscera with possible perforation or hemorrhage, and sepsis. With rapid recognition, management, and prevention of these various complications more than 90% of infants with gastroschisis survive.

The baby should be put in a warm environment immediately after birth. After an open airway and oxygenation are assured—using endotracheal intubation if necessary—the lower half to two-thirds of the baby should be put in a sterile drawstring bowel bag to help decrease heat and evaporative fluid loss and reduce the risk of infection. The use of moist (not dripping wet) saline-soaked gauze over the herniated viscera is acceptable. An intravenous line should be established quickly and broad-spectrum antibiotics (gentamicin and ampicillin) given. In addition, a fluid bolus of 20 cc/kg of 5% dextrose in lactated Ringer's solution should be given over the first hour. In severe hypovolemia, albumin 0.5 g/kg or plasma 10–15 cc/kg can be added to restore intravascular volume. A blood gas analysis should be done when possible and metabolic acidosis corrected with sodium bicarbonate (1 mEq/kg). An orogastric tube should be put in the stomach to prevent aspiration of gastric contents and decrease gut distension caused by swallowed air. A baby prepared in this way usually can be transferred safely to a pediatric surgery center for repair of the defect.

In 40–50% of cases, the gut can be reduced into the abdomen and primary repair of the abdominal wall defect done. This is successful if a small amount of bowel is eviscerated or if the gut is not excessively distended or edematous. In the remainder of cases, the abdominal cavity is too small to accommodate the herniated gut because of the loss of "right of domain." In these instances, construction of a reinforced Silastic silo to partially reduce the viscera is necessary, with subsequent staged reduction of the contents over 7 to 10 days. The abdominal wall then can be repaired. Compression of the inferior vena cava and respiratory distress caused by upward pressure on the diaphragm are two possible complications of either primary or staged reduction which make adequate hydration and meticulous pulmonary care extremely important. Frequently, endotracheal intubation and ventilatory support are necessary in the immediate postreduction period. Because of edema and inflammation within the bowel wall, prolonged adynamic intestinal ileus is common in these infants. A period of 2 to 6 weeks usually is necessary before bowel function is adequate for feeding. Thus, total parenteral nutrition via either the peripheral or central venous route is necessary. Most infants are able to tolerate oral feedings by 1 month, and hospitalization after that is unusual except in complicated cases. With appropriate perioperative support, current survival is 90%.

Congenital Diaphragmatic Hernia

Congenital posterolateral diaphragmatic hernia through the foramen of Bochdalek is the most common surgically correctable cause of severe respiratory distress in the newborn. One in 2200 babies is born with this defect, which in 85% is on the left side, in 13% on the right side, and bilateral in 1–2%. Most infants with diaphragmatic hernia are term babies. Therefore any "large" baby with severe respiratory distress should be suspected of having this congenital defect.

The anomaly forms as the gut makes its normal return to the abdominal cavity from the yolk sac, the diaphragm forms, and the

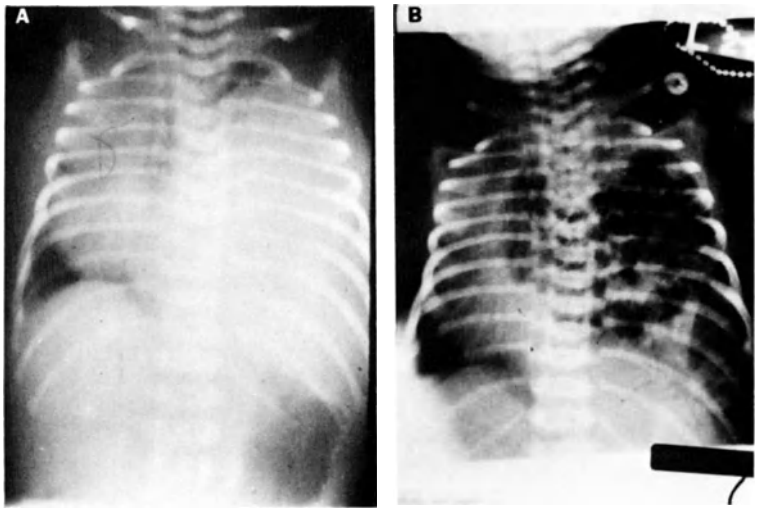

Figure 9-2. A Initial chest radiograph in a newborn with diaphragmatic hernia. Note opacification of the left hemithorax, and shift of the heart into the right chest. Insufficient air has been swallowed by the infant to fill the loops of bowel within the chest. **B** Repeat film 30 minutes later. Air within the loops of bowel now demonstrates the diaphragmatic hernia. Immediate repair was successful.

lung buds develop. Failure of the diaphragm to completely close allow the viscera to herniate into the hemithorax, which prevents the development of the ipsilateral lung. If the mediastinum is shifted, compression of the contralateral lung occurs and interferes with its development as well. The result is moderate-to-severe respiratory distress that usually is present immediately at birth or shortly after. The degree of distress tends to quickly worsen as swallowed air distends the gut within the chest, causing further lung compression and mediastinal shift. Cyanosis, tachypnea, pallor, gasping respirations, retractions, or complete cardiorespiratory arrest are the usual findings as the baby struggles to expand his lungs. Breath sounds usually are absent on the side of the hernia, and heart sounds are shifted to the opposite hemithorax. The baby frequently appears to have a barrel chest and scaphoid abdomen.

The differential diagnosis upon clinical examination will be pneumothorax, chylothorax, meconium or other aspiration syndrome, and congenital cystic lung lesions (lobar emphysema or cystic adenomatoid malformation). If possible, at the first sign of respiratory distress a chest radiograph should be taken before any invasive resuscitative procedures are performed. Occasionally, the film will show an opacified hemithorax if the infant has not swallowed sufficient air to demonstrate the gastrointestinal tract (Fig. 9-2A). If the radiographic findings are confusing, the film should be repeated to further define the problem. Frequently this will show the gut within the chest (Fig. 9-2B).

Newborns with diaphragmatic hernia should be stabilized prior to surgical reduction of the hernia and repair of the defect. Most infants with diaphragmatic hernia benefit from a brief period of preoperative stabilization that should include direct endotracheal intubation with ventilatory assistance.[9] Assisted ventilation with a mask and bag should be avoided because it may introduce excessive amounts of air into the portion of the gastrointestinal tract herniated into the chest, causing further lung compression. After intubation, the child should be rapidly ventilated with 100% oxygen and a blood gas determination made to assess the effectiveness of ventilation (pCO_2 level). Excessive airway pressures should be avoided during ventilation because the development of pneumothorax from lung "blowout" can be fatal in infants with marginal pulmonary reserve. A nasogastric tube to empty the gastrointestinal tract should be placed early during resuscitation. A warm environment is crucial for preserving body temperature. An intravenous line should be inserted quickly and sodium bicarbonate used

to correct any metabolic acidosis. The use of these few extra minutes to stabilize the infant's metabolic status greatly improves his chance of a successful operation and ultimate survival.[9]

The operative approach is straightforward. A transverse or vertical upper abdominal incision is made on the side of the hernia and the viscera gently reduced out of the chest. A tube thoracostomy is inserted through the 5th or 6th interspace and the diaphragmatic defect closed using nonabsorbable sutures. In rare cases the defect is too large for primary closure, and a prosthesis or abdominal wall muscle flap must be used. If the abdominal cavity is small, a ventral hernia can be created by simply closing the skin and subcutaneous tissue over the abdominal viscera. When prolonged, vigorous ventilation is anticipated, a chest tube is placed prophylactically in the contralateral chest to prevent the development of a tension pneumothorax in the event of perforation.

The postoperative management of these infants is demanding and often frustrating. Arterial blood gas monitoring should be done frequently, and appropriate changes in ventilator settings made immediately. Because many of these infants develop pulmonary artery hypertension, pharmacologic adjuncts such as tolazoline, chlorpromazine, and acetylcholine frequently are used in an attempt to decrease pulmonary vascular resistance and the resultant right-to-left shunting through the atrial foramen ovale and patent ductus arteriosus. The efficacy of these agents, however, is not known. Rapid ventilatory rates, as high as 150–200 breaths per minute, also have been used with some success to lower pCO_2 and dilate pulmonary vasculature. As a last resort, extracorporeal membrane oxygenators (ECMO) have been used when death appears imminent.[10] However, few have survived using this experimental procedure. The role of ECMO in the management of infants with diaphragmatic hernia remains unknown.

The overall mortality rate for infants with diaphragmatic hernia who develop respiratory distress within the first 24 hours after birth remains 40–60%, with little or no improvement made in the past 10 to 15 years. On the other hand, infants presenting after the first day of life have a 90% chance of survival. The marked difference probably is the result of this latter group's cardiopulmonary reserve and smaller degree of pulmonary hypoplasia. It is hoped that continued improvements in postoperative care will decrease the mortality in infants with this defect.

Exstrophy of Cloaca and Bladder

Exstrophy of the bladder and cloaca are congenital malformations of the lower abdominal wall that result from the failure of components of the caudal fold to develop. Although these defects are thought too complex to be the result of a single embryologic event, many authors feel they are caused by an incomplete fusion of lateral mesoderm that comprises the genital tubercle, anterior bladder walls, the symphysis pubis, and the lower abdominal wall.[11] These defects are represented in varying degrees of severity within a spectrum of anomalies that also may include malformations of the sacrum, neural canal (myelomeningocele), lower extremities, and genitalia. In both defects the anterior (ventral) bladder wall is absent. Males with exstrophy of the bladder also frequently have epispadias. To simplify the anatomy, exstrophy of the cloaca can be considered a bladder exstrophy, with the addition of an omphalocele, imperforate anus, microcolon, and a vesicointestinal fissure, a peculiar opening of the gastrointestinal tract between the two halves of the bladder (Fig. 9-3).

The immediate postpartum care of infants with exstrophy is similar to that for infants with omphalocele. Fluid maintenance, heat preservation, and a clean, aseptic environment are important. An intravenous line should be established and broad-spectrum antibiotics given. Moist sterile gauze should be placed over the abdominal defect and the bowel bag (as outlined in the section on omphalocele) reserved for those infants with cloacal exstrophy and large omphalocele. An orogastric tube is advisable until patency of the gastrointestinal tract is ensured.

Because these infants require demanding intraoperative and postoperative management, they should be transferred to a pediatric surgical/urologic center. Many infants born with these defects are premature, and the potential problems of prematurity (respiratory

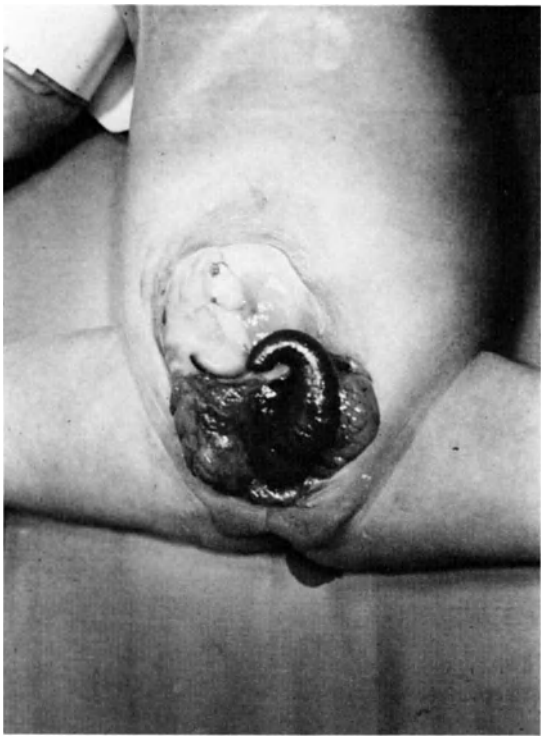

Figure 9-3. A newborn with exstrophy of the cloaca. An omphalocele at the most cephalad portion of defect and two bladder halves with a centrally placed vesicointestinal fissure are seen. Staged complete repair was successful.

distress, hyperbilirubinemia) must be considered. In addition, the genitalia of infants with both defects, particularly those with cloacal exstrophy, frequently are significantly deformed, making chromosomal analysis mandatory. An evaluation by a multidisciplinary gender assignment committee, which usually is found in children's hospitals, also is routine. Obviously, sex assignment should not take place until this evaluation is completed, and this should be fully explained to the parents shortly after birth.

The operative approach to these infants depends upon the embryologic defects. Thus, treatment is highly individualized. Infants with exstrophy of the bladder but with an intact gastrointestinal tract can undergo staged reconstruction of the bladder and genitalia either early in life or later. Previously, permanent urinary diversion with ureterosigmoidostomy or ileal loop procedures were done in combination with cystectomy and genital reconstruction. However, pediatric urologists and surgeons now take a more aggressive approach to bladder salvage by "turning in" the lateral aspects of the bladder wall anteriorly, thereby creating a closed bladder. This usually is combined with bilateral iliac osteotomies so that the pubic symphysis can be repaired. In those children with severe epispadias and absent urethra, a urethra can be formed by tubularizing a portion of the bladder, and later on creating an artificial sphincter.

The management of infants with cloacal exstrophy is more complex. The initial problems of omphalocele and imperforate anus require surgery shortly after birth. Repair of the omphalocele (which usually can be done primarily), reduction of the vesicointestinal fissure, recentralization of the right and left hemibladders, and colostomy are done at the same time. Resection of duplications of cecum, colon, or appendix—common findings in these infants—also can be done at this time. After the first stage is completed, the patient is left with a bladder exstrophy that can be treated surgically in the ways outlined above. Again, each infant's problems are unique and treatment should be tailored to the specific situation.

There has been no long-term follow-up for cloacal exstrophy because until recently the defect was considered incompatible with life. Recent experience, however, suggests that aggressive surgical repair is fully warranted. A 50% mortality rate reported in 1979[11] probably is less now because of improved intraoperative and postoperative management.

Simple bladder exstrophy without cloacal deformity has a brighter prognosis. A recent large series[12] showed a 4% mortality, 80% normal upper urinary tracts, and more than 50% urinary continence at 5-year follow-up. Further improvements in survival and quality of life for these infants clearly are forthcoming.

Sacrococcygeal Teratoma

Sacrococcygeal teratomas are large, firm tumors that arise from the coccyx or anterior sacrum. They typically extend posteriorly, laterally into the gluteus muscles, and cephalad between the sacrum and rectum. The

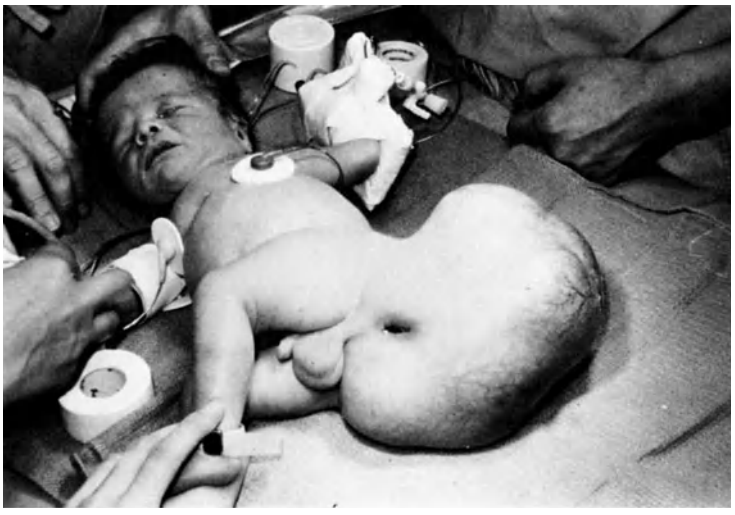

Figure 9-4. Massive sacrococcygeal teratoma in a newborn. Note anal opening at the base of the tumor. One-stage resection of the entire tumor was performed.

tumor may be entirely external or may contain pelvic and even intraabdominal extensions. These tumors can reach massive proportions, at times approaching the baby's own length and weight (Fig. 9-4).

The incidence of sacrococcygeal teratoma is one in 35,000 births, with females accounting for 60–75% of all cases. Approximately 60% of tumors are diagnosed at birth, while the remainder are discovered as late as adulthood. Early diagnosis depends on the extent of tumor visible on the exterior. More than 10% of tumors are presacral and intrapelvic, discovered only by rectal exam or lower abdominal palpation. Early diagnosis is desirable because there seems to be a true malignant degenerative potential of the tumor in infants older than 4 months.

Because the external tumor is often massive, a difficult delivery and dystocia frequently occur. In the largest series of sacrococcygeal teratomas reported (the Surgical Section Survey of the American Academy of Pediatrics),[13] 9% of 405 infants required delivery by cesarean section. Ninety-two percent of these were term babies.

Trauma at birth to the tumor and baby can be a major cause of morbidity and mortality. Laceration or contusion of the tumor resulting in massive hemorrhage is a risk during the vaginal delivery of infants with moderate or large tumors. Most infants who undergo a safe delivery appear asymptomatic. Although rare, symptoms related to obstruction of the rectum or lower urinary tract from presacral and intrapelvic extensions also may be present early.

The early management of these infants includes putting the infant on its side, maintaining its temperature, and inserting an intravenous line. A blood specimen for typing and cross-matching should be obtained early because contusion to the tumor during delivery may cause occult bleeding within the mass. Preoperative blood specimens also should be taken for α-fetoprotein and human chorionic gonadotropin, two tumor markers that are frequently elevated preoperatively but fall to normal after the tumor is excised. These markers also are useful in follow-up because an increasing level is excellent evidence of recurrent tumor or the development of metastases. If the rectum is severely compressed or obstructed, an orogastric tube should be placed. Because the majority of infants are term and have a low incidence of other anomalies, no other specific care is necessary prior to surgical removal of the tumor.

The surgical approach depends on the extent of the tumor. The rare newborn with a large intraabdominal or pelvic extension should have an abdominal exploration first to dissect and "free up" that portion of the tumor. For the excision of posterior tumors, the infant must be prone on the operating table, after appropriate intravenous and intra-

arterial lines have been secured. A transverse "chevron" or longitudinal incision is used and the capsule of the tumor dissected directly. Careful dissection of tumor off the rectum is necessary to avoid injury. A finger or balloon catheter (Foley) within the rectum frequently will facilitate this dissection. The coccyx must be removed en bloc with the specimen to deter recurrence. Likewise, the tumor capsule should not be entered so as to prevent tumor spill. Recurrences frequently are malignant even when the primary tumor was benign, making it imperative that all of the tumor be removed during the first operation.

After the tumor is removed, suction catheters are left in place for several days to drain the large cavity. Bowel and bladder functions usually return promptly, and the infant begins feeding within 2 days.

The results for resection of benign tumors are excellent. The recurrence rate is low. Recurrence usually can be detected early by serum α-fetoprotein determinations before the tumor mass is felt. Unfortunately, the outlook for malignant tumors is not as favorable. A 60% mortality rate was noted in the American Academy of Pediatrics survey, with a mean life span of only 10 months after diagnosis.[13] It is hoped that more aggressive multimodal chemotherapy with drugs such as cis-platinum and bleomycin that are active against germ cell tumors will improve survival. Because the incidence of malignancy increases dramatically after the infant is 3 months old, earlier diagnosis and resection is critical to survival.

Congenital Lung Cysts

Congenital cystic lesions of the lung, which include congenital lobar emphysema, cystic adenomatoid malformation, and true lung cysts, can present shortly after birth with respiratory distress that at times is severe. These anomalies form as the lung buds develop from the primitive foregut. Because early operative intervention often is critical for survival, rapid recognition of these conditions and early initiation of therapy are extremely important.

These infants frequently have signs of respiratory distress shortly after birth, the amount of distress depending upon the size of the lesion and the degree of lung compression. The distress may be mild initially but progress raidly over several hours as air becomes trapped in the cyst, causing increasing lung compression. Tachypnea, grunting, cyanosis, and sternal retractions are early indications of respiratory difficulty. Breath sounds on the side of the lesion are poor or even absent, which can lead to a mistaken diagnosis of pneumothorax. A chest radiograph should be taken before doing a needle or tube thoracostomy.

The radiographic appearances of true lung cyst and congenital lobar emphysema are

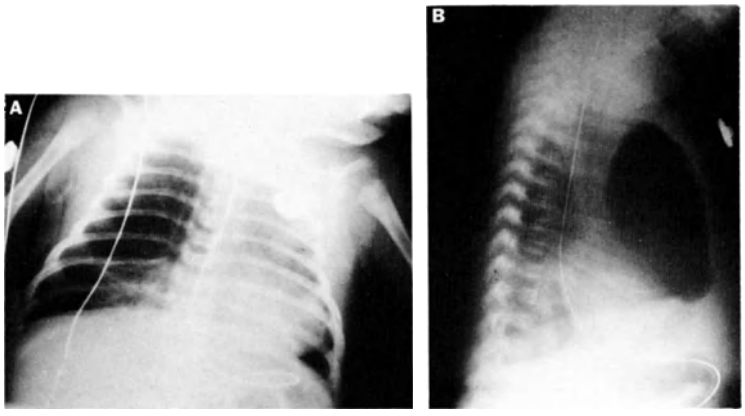

Figure 9-5. Posteroanterior and lateral chest radiographs in a newborn with respiratory distress. There is a hyperlucent right hemithorax with slight shift of the mediastinum to the left. On the lateral view, a large lucent area just below the sternum is seen. At operation, right middle lobectomy was performed for congenital lobar emphysema.

similar. Unilateral hyperlucency, often with lung compression and mediastinal shift, is the typical picture (Fig. 9-5). This can be confused with pneumothorax, but careful inspection of the film usually will reveal a visible cyst wall. Cystic adenomatoid malformation, on the other hand, is a hamartomatous lesion that has both solid and cystic areas. On radiography this lesion's appearance has been described as a "Swiss cheese wedge." In all lesions, a single upper lobe usually is affected. In congenital lobar emphysema, the order of most frequent involvement is the left upper lobe, right upper lobe, and right middle lobe.

The therapy for these various cystic lesions is operative resection, sparing as much normal lung as possible. Nonoperative therapy has an unacceptably high mortality in these infants,[14] whereas resection can be done with low morbidity and mortality. For solitary lung cysts, excision usually is all that is necessary. Congenital lobar emphysema and cystic adenomatoid malformation usually require a lobectomy for complete removal. An occasional case of congenital lobar emphysema is the result of extrinsic compression—usually from a mediastinal bronchogenic cyst—on the bronchus supplying that lobe. The majority of these lesions, however, have no specific etiology.

The long-term results after resection are excellent. Lung tissue has the ability to grow for the first few years of life. Thus, the pulmonary function in these children is excellent.

Summary

The congenital anomalies discussed in this chapter are the most frequently encountered problems that can be life threatening if not recognized and treated early. With ultrasound and other imaging techniques continuing to improve fetal diagnosis, prompt perinatal care should improve survival rates in the seriously ill neonate with congenital malformations. Early recognition and resuscitation, frequently by the physician who delivers the child, will continue to play a major role in the survival and improved quality of life of these newborns.

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Gynecologic Surgery in the Adolescent 10

Thomas R. Weber and Jay L. Grosfeld

Practitioners involved in the care of pediatric and adolescent patients are frequently called upon to help in the diagnosis and management of female pelvic disorders. The differentiation between medical and surgical causes of pelvic symptoms such as pain, constipation, and diarrhea and the appropriate workup and prompt initiation of therapy demand a knowledge of the most common disorders that produce such symptoms. The purpose of this chapter is to review the differential diagnosis of abdominal and pelvic pain and other pelvic symptoms in children and adolescents, to examine the diagnostic modalities available to help differentiate between the various causes of pelvic disorders, and to discuss the basic surgical approaches to pelvic abnormalities in the female pediatric and adolescent patient.

Differential Diagnosis

The most common disorders that produce pelvic pain in the child include gastroenteritis, urinary tract infection, constipation, pelvic inflammatory disease, mesenteric adenitis, inflammatory bowel disease, ovarian torsion, and appendicitis.[1] The following general discussion of these various disorders will provide a differential diagnosis for pelvic pain in pediatric and adolescent patients.

Gastroenteritis

This is probably the most common reason for an emergency room visit prompted by abdominal or pelvic pain.[2] Fever, vomiting, diarrhea, anorexia, and abdominal pain may all be present in various combinations, and the entire clinical picture may appear identical to appendicitis, especially in the younger child.

Urinary Tract Infection

Urinary tract infection may be present in female patients of any age, although it is probably more prevalent in the older child and adolescent. High fever, flank pain, bilateral or midline tenderness, dysuria, and pyuria will alert the clinician to this diagnosis.

Constipation

Constipation is one of the most common causes of abdominal pain in children of all ages. A carefully obtained history, palpation of a stool-filled colon on abdominal examination, and relief of pain with an enema all help to make this diagnosis.

Pelvic Inflammatory Disease

Pelvic inflammatory disease has become more common over the past several years in the sexually active adolescent. The onset of pain is often preceded by menses, and the pain begins in the lower quadrants. Severe cervical and adnexal tenderness, purulent vaginal discharge, and high white blood cell count and sedimentation rate are typical for pelvic inflammatory disease. Differentiating between pelvic inflammatory disease and appendicitis

is extremely difficult; not infrequently the diagnosis is made by removal of a normal appendix.

Mesenteric Adenitis

Enlargement of mesenteric lymph nodes after a viral illness is common and can produce right lower quadrant pain.[3] It is probably best to make this diagnosis only *after* appendectomy.

Inflammatory Bowel Disease

In approximately 10% of cases, ulcerative colitis will present as an acute illness without previous symptomatology, but this presentation usually includes a fulminant course of bloody diarrhea, high fever, and abdominal distension rapidly progressing to inanition.[4] However, most cases have an insidious onset that is easily differentiated from other disorders.[5] On the other hand, Crohn's disease has an extremely variable presentation that may include recurrent abdominal colic, diarrhea, acute abdominal pain mimicking appendicitis, and growth retardation.[6] Extraintestinal manifestations (arthritis, skin lesions, uveitis, liver disease, stomatitis) are frequently present, occasionally even before the onset of intestinal symptoms, and may be a clue to the diagnosis.

Ovarian Torsion

An extremely abrupt onset of unilateral pelvic pain in the adolescent female is suggestive of ovarian torsion.[7,8] Frequently an ovarian cyst is present which enlarges the ovary sufficiently to allow twisting.[9] Rarely, a cystic ovarian teratoma (dermoid) in a younger child will present initially as torsion.[10,11]

Appendicitis

Acute inflammation of the appendix can occur at any age, from newborn to the very elderly. Numerous monographs through the years have reaffirmed the diagnostic challenge of appendicitis, the various clinical pictures which it can present in childhood, and the serious sequelae if the appendix perforates.[3,12–14] A normal appendix removal rate of 3–5% is still acceptable in this modern era of sophisticated diagnostic procedures,[15] while there can be no excuse for a patient perforating while under the observation of a physician. Even with recent advances in antibiotic and intensive care support, a mortality rate in perforated appendicitis of 0.1–1.0% persists in most children's hospitals, whereas the mortality rate from removal of a normal or nonruptured inflamed appendix approaches zero.

Evaluation

The evaluation of the pediatric patient with pelvic pain or other symptoms begins with a complete history and physical examination. Table 10-1 summarizes some aspects of the history and physical examination of these various disorders. In utilizing a table such as this, several factors must be kept in mind. First, each patient is unique; the "classic" presentation of a specific disease is rarely seen. Anatomic variations; differing responses to pain and tenderness; fear of hospitals, physicians, and nursing personnel; unpleasant diagnostic studies; and fear of punishment may have profound modifying effects on all of the signs and symptoms presented. Because younger childeren frequently cannot or will not relay accurate information concerning the onset of symptoms, localization of pain, and chronicity, the clinician must obtain such information secondhand from anxious and sometimes confused parents. In spite of these drawbacks, Table 10-1 is useful in emphasizing that the history and physical examination of the patient remains the most important part of the diagnostic workup. There are enough unique features for each disorder to allow a definite clinical diagnosis in most instances.

Several aspects in the history of the onset of pain deserve emphasis. In appendicitis, the pain is virtually always periumbilical initially, only later migrating to the right lower quadrant as the parietal peritoneum becomes irritated. Vomiting usually comes after the onset of pain. In contrast, children with gastroenteritis may have a similar abdominal pain pattern, but the pain doesn't localize well and frequently occurs after vomiting rather than before. With urinary tract infection, the pain is more flank or deep pelvic in origin, and is

Table 10-1. Signs and Symptoms of Pediatric Pelvic Disorders.

	Urinary Tract Infection	Appendicitis	Gastroenteritis	Constipation	Inflammatory Bowel Disease	Ovarian Torsion
Chronicity	Acute or chronic	Acute	Acute	Chronic	Chronic	Very acute
Diarrhea	None	Mucous, low volume	Frequent, high volume	None	Frequent, usually mucous or bloody	None
Vomiting	Infrequent	Frequent, after pain starts	Frequent, before pain starts	None	Infrequent	Frequent, with onset of pain
Pain pattern	Pelvic, frequently bilateral	Umbilical, migrating to right lower quadrant	Diffuse	Bilateral lower quadrants	Diffuse, may localize to pelvis	Diffuse
Tenderness	Mild	Moderate to severe	Mild to moderate	Mild or none	Mild to moderate	Moderate to severe
Other signs or symptoms	Dysuria	May have dysuria	None	None	Weight loss, joint pains, malaise	None
Localization of pain	Poor	Right lower quadrant	Diffuse	Poor	Diffuse	Localized to right or left pelvis
Peritoneal signs	Absent	Present	Mildly present	Absent	Present	Present
Fever	Elevated	Elevated	Elevated	Normal	Normal to slight elevation	Normal

often preceded by dysuria. The pain associated with constipation and inflammatory bowel disease (ulcerative colitis and Crohn's disease) is usually insidious in onset, chronic or intermittent over a period of weeks or months, and in the case of inflammatory bowel disease associated with so many other signs and symptoms that confusion rarely exists. Torsion of an ovary represents an abrupt interruption in the blood supply to the ovary and fallopian tube that produces intense pain and vomiting. Frequently the patient or her family can tell the physician the exact time the pain began. The severity of the pain is out of proportion with the physical findings, and vomiting accompanies the onset of pain.

The successful physical examination of the pediatric patient is considerably different than in the adult. Because of the child's feelings of fear, guilt, or pain, examination for abdominal tenderness, peritoneal signs, or abdominal mass can be frustrating and nonrewarding. Allowing younger children to localize an area of maximal tenderness by using their own hands is sometimes useful, whereas older children will point to the spot. In all cases the most unpleasant or painful part of the examination, such as palpation directly over the area of pain or the rectal exam, should be done after a complete history is obtained and at the end of the physical examination. The administration of Seconal (1 mg/kg) intramuscularly will provide sedation without analgesia, so that a more thorough evaluation can be performed.

Frequently the initial physical examination is nonspecific or confusing; a repeat examination 30 to 60 minutes later is more definitive. Admission to the hospital for several examinations spaced over a period of a few hours is sometimes necessary.

In eliciting signs of peritoneal irritation, the stretch receptors in the parietal peritoneum respond to the rate of stretching. Thus, slow deep palpation in the area of question followed by quick release will elicit either a visible

wince or verbal expression of pain, or both. As peritoneal irritation becomes more severe, there will be guarding (voluntary stiffening) and spasm (involuntary rigidity) within the rectus muscle, both of which are readily apparent on palpation of the abdomen. Rebound tenderness, guarding, and spasm are evidence of severe intraperitoneal irritation and are usually indicative that a surgical process is present. Blood, fecal material, and pus are all extremely irritating to the parietal peritoneum, producing these physical signs.

No physical examination in a child with pelvic pain is complete without rectal examination. Because of the shortness of rectal length, a finger gently inserted through the rectum can frequently explore the entire pelvis; pelvic masses, areas of tenderness, and organomegaly can be readily found. In the adolescent female with suspected pelvic inflammatory disease, rectal examination seems to produce less anxiety and is usually less threatening and uncomfortable for the patient. More gentle palpation of the inflamed cervix can be performed through the rectal wall in this manner.

Laboratory studies can be helpful in differentiating the various causes of pelvic pain. Urinalysis is perhaps the most important study; if more than 30 white blood cells per high power field are found, urinary tract infection is suggested and should prompt a Gram's stain and urine culture. If purulent material is expressed from the vagina, suggesting pelvic inflammatory disease, it too should be cultured and Gram-stained. If either urinary tract infection or pelvic inflammatory disease is suspected, one or two doses of intravenous antibiotics can be administered, followed by reassessment of the abdominal examination. In most cases significant improvement in physical findings will occur in these infectious processes, while surgical lesions such as appendicitis will progress.

The white blood cell (WBC) count and cell differential are elevated in most cases involving inflammatory or infectious processes, and therefore are not particularly helpful. In addition, many cases of appendicitis have a normal or slightly decreased WBC count, creating additional confusion. In general, a WBC count greater than 20,000 suggests urinary tract infection or pelvic inflammatory disease rather than appendicitis, unless the latter is perforated. The WBC count is usually normal or slightly elevated in constipation, inflammatory bowel disease, and ovarian torsion.

Radiologic Evaluation

With the onset of newer imaging modalities, the radiologic evaluation of the patient with pelvic pain can become complicated, time consuming, and expensive. However, it must be kept in mind that the disorders outlined in this chapter are primarily clinical diagnoses, and radiologic procedures are utilized in confusing cases or where clinical evaluation is difficult, such as in brain-damaged children or the very young child.

Supine and upright abdominal radiographs should be the initial radiologic studies obtained. Significant findings related to pelvic pathology include abnormal gas patterns, air–fluid levels (localized paralytic ileus), peritoneal fluid, scoliosis toward the side of an inflammatory process, psoas muscle obscuration, thickening of abdominal wall, presence of fecalith, and signs of a mass or abscess (Figs. 10-1–10-3).[16]

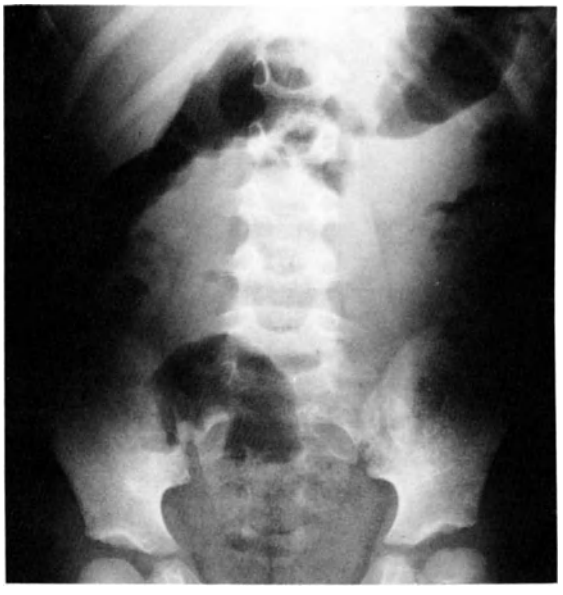

Figure 10-1. Upright abdominal radiograph in a 14-year-old girl with signs and symptoms suggesting appendicitis. Note the "sentinel loop" of small bowel, with an air–fluid level in the right lower quadrant. Acute appendicitis was confirmed surgically.

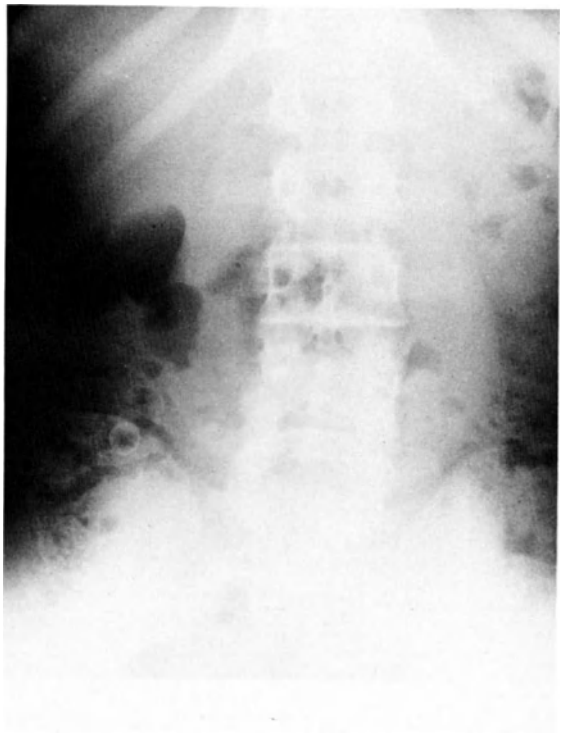

Figure 10-2. Supine abdominal film in a 16-year-old girl with right lower quadrant tenderness. A large, round appendicolith is seen in the right lower quadrant, associated with obliteration of the psoas muscle shadow and scoliosis to the right. An acutely inflamed appendix with appendicolith was removed.

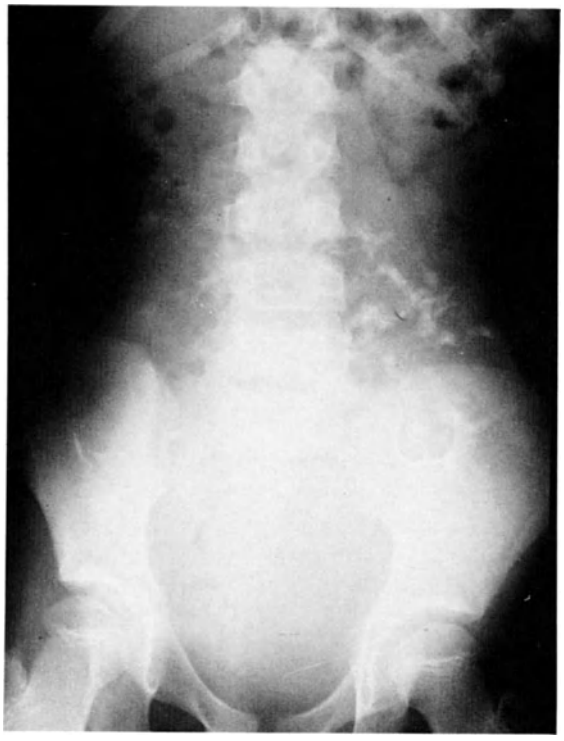

Figure 10-3. Pelvic radiograph in a 13-year-old girl with abrupt onset of midline pelvic pain. Note the scattered calcification in the region of the left ovary, and the "mass effect." Torsion of an ovarian teratoma was found at surgical exploration.

Contrast studies, primarily of the lower gastrointestinal tract, are occasionally needed when plain films are nondiagnostic. In the workup of patients with right lower quadrant pain in whom physical examination is not definitive for appendicitis, barium enema can be helpful.[17] If the appendix fills with barium, appendicitis is excluded as a diagnosis. On the other hand, nonfilling of the appendiceal lumen with barium, or the presence of a mass (Fig. 10-4), are signs suggestive of appendicitis. In addition, the diagnosis of inflammatory bowel disease, either ulcerative colitis or Crohn's disease, can be made by barium enema (Figs. 10-5 and 10-6). In inflammatory bowel disease and other severe inflammatory disorders such as salmonella/shigella gastroenteritis, extreme care must be utilized in performing the barium enema; perforation may result if too much pressure is used to fill the colon with the contrast material. Severe spasm in the rectosigmoid which prevents total filling of the colon is strongly suggestive of significant colonic inflammation in a child, and persistence in attempting to fill such a colon will frequently lead to disaster.

The role of ultrasound and computed tomography is less clear than that of plain films and contrast studies. In the patient with chronic pain and the presence of a mass on physical examination, one or both of these studies might be useful in deciding what organ is involved, whether the mass is cystic or solid, and directing further workup and therapy. For the patient with acute pelvic pain, these studies have a limited role and are usually not needed to make a diagnosis.

Surgical Approaches

Strong consideration should be given to using a transverse incision on the pediatric or adolescent patient undergoing pelvic surgery.

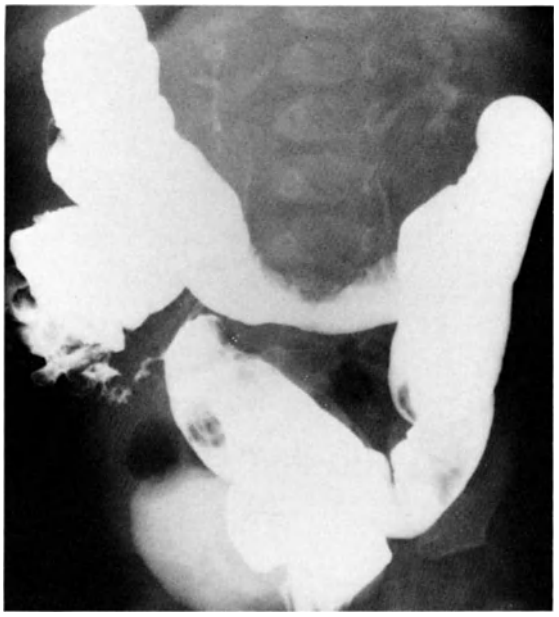

Figure 10-4. Barium enema in a child who subsequently was found to have perforated appendicitis. The cecum fills poorly and has a mass indenting its medial wall. The appendix did not fill, and there is diffuse spasm and irregularity in the terminal ileum.

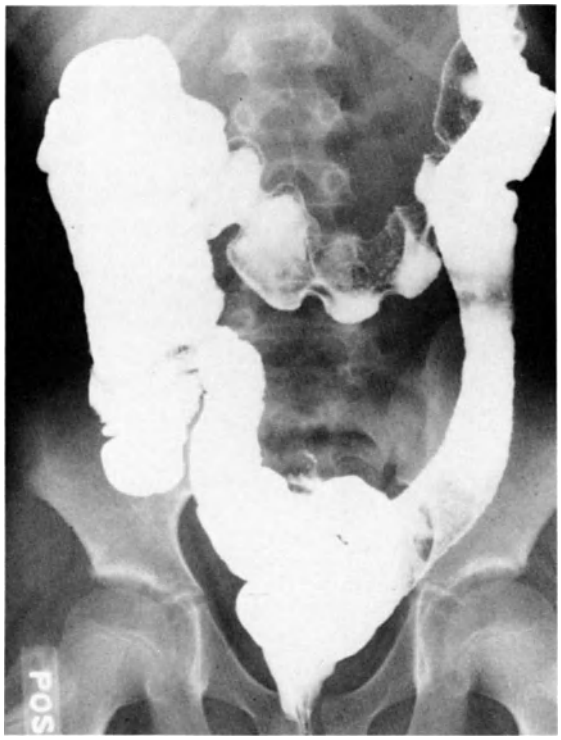

Figure 10-5. Barium enema in a child with a 3-day history of abdominal pain and diarrhea. The mucosa in the left colon is irregular, and there is a "pipe-stem" appearance to the left colon due to shortening from ulcerative colitis.

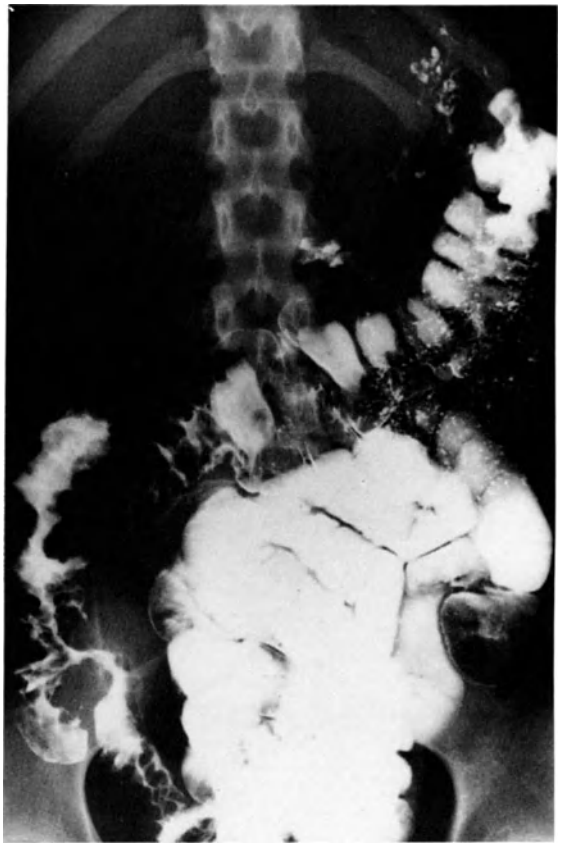

Figure 10-6. Barium enema in a 10-year-old child with right lower quadrant tenderness, fever, and a mass felt on rectal exam. The entire right colon and terminal ileum are diffusely narrowed and irregular, with near total obstruction at the ileocecal value. Further history revealed weight loss and arthritis, confirming the suspicion of Crohn's disease.

A transverse incision is cosmetically more acceptable, can be kept below the bikini line in many instances, affords excellent exposure, and heals more soundly than a midline incision. If a midline incision is desired, a Pfannenstiel approach, using a transverse skin incision, and midline fascial opening is satisfactory. In any case, careful hemostasis and gentle handling of tissues is the best insurance against wound infection and its associated complications. A urinary catheter should be placed prior to every pelvic surgical procedure, but is not routinely needed for appendectomy.

During the procedure, conservativeness and restraint should be practiced if at all possible. Limited resections, preservation of normal tissue and organs, and debridement and

drainage rather than removal are the principles that should be applied. Since the lesions discussed in this chapter are not malignancies, there is very little indication for radical resections. In the following discussion, each disorder requiring surgery will be examined with these principles in mind.

In unruptured appendicitis, simple removal of the appendix is all that is necessary. In contrast, the perforated appendix with abscess formation is more complicated. Appendectomy, irrigation of the abscess cavity, and placement of drains is the most efficacious way of managing this common disorder. If the perforation is longstanding, significant inflammatory response within the organs forming the abscess cavity (loops of bowel, bladder, uterus, fallopian tube, and ovary) and the formation of a pelvic phlegmon are common, making removal of the appendix extremely difficult and risky. In these instances, simple irrigation and drainage of the cavity is acceptable, with interval appendectomy performed 4 to 6 weeks later. At that time, removal of the appendix is usually straightforward.

In cases of pelvic inflammatory disease and tuboovarian abscess, debridement, irrigation, and drainage combined with high dose antibiotic therapy are preferred to bilateral salpingo-oophorectomy, the latter (frequently combined with hysterectomy) being the common recommendation for adults with this disease. If sepsis persists reexploration several days later is preferable to more radical procedures initially. Many children will have only unilateral tuboovarian abscess, in which case a single salpingo-oophorectomy can be utilized. Obviously the safety of the child must be kept in mind whenever these conservative approaches are used for pelvic infectious processes.

For cases of torsion of the ovary, the fallopian tube and ovary are frequently necrotic and infarcted by the time the lesion is discovered, and salvage is usually not possible (Fig. 10-7). However, a trial of detorsion, with 15 to 20 minutes of observation of the appearance of the ovary, might be advisable if the onset of the torsion is less than 4 hours prior to exploration. The use of the Doppler probe intraoperatively for the detection of pulses within the ovary is also useful. In all cases of ovarian torsion secondary to cyst formation, the contralateral ovary should be carefully inspected, and cystic lesions within that ovary extirpated. However, bilateral oophorectomy should be avoided.

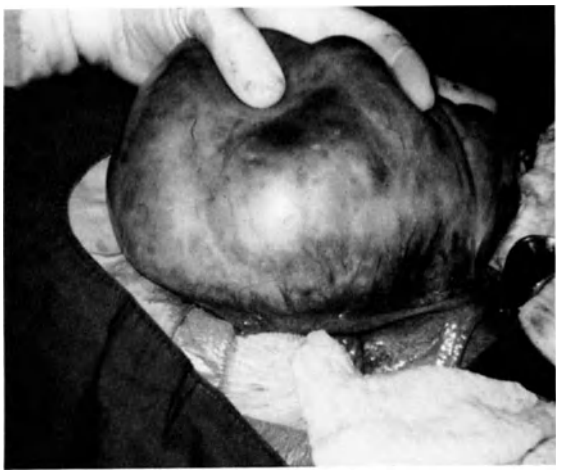

Figure 10-7. Operative findings of patient whose radiograph is shown in Fig. 10-3. A large ovarian cystic teratoma which had undergone torsion around the fallopian tube was resected successfully. Note several areas of hemorrhage and ischemia on the surface of the cyst.

When inflammatory bowel disease is unexpectedly discovered at the time of pelvic exploration, the best approach in most circumstances is to simply close the incision and perform a more complete workup, including contrast radiologic procedures and proctoscopy and biopsy. This is particularly true for Crohn's disease, where even minor manipulation of the bowel may lead to acute exacerbation of the disease.[4] If enlarged lymph nodes are present within the mesentery of the affected bowel, biopsy of one of these may demonstrate granulomas histologically, confirming Crohn's disease, but under no circumstances should the bowel be biopsied in an area of active inflammatory process. In addition, appendectomy in patients with Crohn's disease is not advisable unless the cecum is completely normal in appearance. Appendectomy in patients with active Crohn's disease in the cecum usually results in the formation of an enterocutaneous fistula that can be difficult to manage.[18]

Wound Closure

Closure of the wound can be performed in a wide variety of ways, using any one of an ever-increasing selection of suture materials. In

general, absorbable suture (catgut, polyglycolic acid) should be used to close the peritoneum, usually in a running fashion. The fascia should be closed with a longer-lasting suture material, as the strength of the wound closure relies on adequate fascial apposition. Monofilament suture is used for operative procedures involving drainage of abscesses or other gross contamination, while polyfilament suture is satisfactory for clean cases. In general, permanent suture material is used for fascial closure, although many surgeons have had excellent results with long-lasting absorbable suture such as polyglycolic acid and polydioxanone. These latter materials have the advantage of eventually disappearing, decreasing the risk of the development of troublesome suture granulomas months or even years after the procedure. Because of the paucity of subcutaneous fat in most children, the knots of the fascial closure should be inverted and buried under the fascia itself. This seems to decrease the incidence of painful subcutaneous knots. An interrupted suture technique, rather than a running suture, is the safest approach for fascial closure.

Skin closure is also a matter of personal preference for the surgeon. In most cases involving gross contamination, the skin and subcutaneous tissue should be left open to heal by secondary intention or be closed with tapes or suture 3 to 5 days later. Saline "wet to dry" dressings, changed two or three times per day, will gently debride the wound, allow drainage of purulent material, and prepare the wound for later closure. If desired, this technique can be continued until the wound is completely healed. As an alternative, very loose closure with monofilament suture can be used, with careful observation postoperatively for the development of deep wound infection. For clean cases, running or interrupted absorbable suture (plain or chromic catgut) in the subcutaneous tissues will help relieve tension on the skin sutures and make for a more cosmetically satisfactory skin closure. Although skin sutures or skin staples can be used to approximate the skin edges, subcuticular sutures, either runninng or interrupted, using absorbable suture obviate the need for later suture removal (frequently a traumatic event for a child), and generally make a smaller surgical scar. The use of paper tapes over the wound after the subcuticular closure adds strength to the suture line and allows more exact approximation of the skin edges. An occlusive dressing over the wound for 24 to 48 hours completes the procedure.

Drains

The use of postoperative drains in cases involving drainage of abscess is a well-accepted adjunct to overall surgical care. Ruptured appendix with abscess formation and tuboovarian abscess associated with pelvic inflammatory disease are the most common indications for postoperative drains in pediatric pelvic surgery. Either nonsuction (Penrose) or suction drains can be used, but the drain should be soft and pliable to limit the risk of perforation through inflamed bowel wall adjacent to the abscess cavity. The drains should be placed in the most dependent portion of the abscess cavity, or if the abscess is not located deep within the pelvis, a second drain can be placed in this latter position to help prevent the development of a postoperative pelvic abscess. The drains can be exteriorized either through the wound or through separate stab incisions; the latter approach obviously has the disadvantage of creating additional scars, whereas the former may lead to wound dehiscence and evisceration. If the drains are brought out through the wound, placing them in the most lateral aspect of the wound is the best insurance against evisceration. The drains are usually removed after 2 to 4 days.

Summary

Lower abdominal and pelvic pain and other symptoms are common in children and can be caused by a variety of disorders. Thorough history and physical examination should develop a differential diagnosis which can be further narrowed by radiologic procedures. The basic surgical approach to the pediatric patient should be one of conservative resections, keeping in mind that the child faces 50 to 70 years of lifetime after the operation, mandating careful thought before radical procedures are undertaken.

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Gynecologic Neoplasms 11

John A. Carlson

Malignant neoplasms are very uncommon in children. Annual incidence rates range from 124.5 per million in white children to 97.8 per million in black children.[1] Although the distribution of childhood malignant tumors varies with age, race, sex, and geography, leukemias are the most common, followed by central nervous system tumors, lymphomas, neuroblastomas, soft tissue sarcomas, Wilm's tumors, and bone tumors, respectively.[1,2] Collectively, these cancers are the second most common cause of death in children under 18 years.

Only 2–5% of malignant pediatric tumors occur in the female reproductive organs. Of these, ovarian cancer is the most frequent (65–70%), although cancers also arise in the vagina, vulva, or uterus.[1–4] The ovarian malignancies are most likely to occur at puberty, whereas other reproductive tract tumors appear in younger children and infants. Although most gynecologic cancers appear to be random occurrences, there are several childhood syndromes in which they are more common. For example, those with Peutz-Jeghers syndrome are at an increased risk for a particular sex cord tumor, and children with dysgenetic gonads develop gonadoblastomas and other malignant germ cell tumors. The in utero exposure to diethylstilbestrol has been associated with an increased risk of clear cell adenocarcinoma of the cervix.[5,6]

Ovarian Neoplasia

Ovarian cancer is the most commonly found gynecologic malignancy in childhood and adolescence. Understanding this neoplasm has been complicated by the variety of ovarian tumors, the difficulty in differentiating between physiologic changes and neoplasia, and the relative inaccessibility of the ovary. The following brief discussions of embryology and anatomy are intended to help simplify this subject.

Embryology

Embryology is the key to understanding ovarian neoplasms. During the fourth week of embryonic life, a pair of longitudinal ridges (gonadal ridges) arise between the dorsal mesentery and the mesonephros. The ridges form from a condensation of mesenchyme and a proliferation of primitive coelomic epithelium. During the sixth week, the germ cells, which apparently arise in the yolk sac near the allantois, migrate to the gonadal ridge. As the coelomic epithelium proliferates and becomes the more prominent component of the ovary (the future cortex), cords of epithelium interdigitate with the mesenchyme forming the sex cords. With further differentiation, the sex cords eventually separate from the surface epithelium, while the germ cells multiply and establish permanent follicles. Some sex cord epithelial cells that grow deeper into the mesenchyme do not contain germ cells and eventually regress, persisting as rudimentary tubules in the mesenchyme, the future medulla of the ovary. By the 12th week of development, the gonad is recognizable as an ovary that has been developed from

coelomic epithelium, mesenchyme, and germ cells.[7]

Anatomy

The developing ovary lies between the 10th and 12th thoracic segments and is suspended from the posterior abdominal wall by the infundibulopelvic ligament, which contains vessels and nerves. Later, the ovary is drawn to a more caudal position, and is eventually located on either side of the uterus in the ovarian fossa in close proximity to the iliac vessels and the ureter. The ovary does not descend into the true pelvis until after puberty. Thus, its abdominal location in the prepubescent patient may lead to some difficulty in diagnosing ovarian neoplasms.[8]

In the normal adolescent or preadolescent the uterus usually is quite small, midaxial, and easily palpated. The fallopian tube is not palpable, and the ovary may vary. Prepubertally the ovary is approximately 1.5–2 cm in length and 0.5 cm in width. After menarche the ovary is much larger, measuring 3–3.5 cm in length and 1.5–2 cm in width, with a thickness of approximately 1.0–1.5 cm. During the reproductive years the size of the ovary varies with the phase of the menstrual cycle, but the normal ovary rarely exceeds 6.0 cm in diameter.[3,8]

The blood and nerve supply to the ovary originate between the 10th and 12th thoracic vertebrae in close proximity to the kidney. The ovarian arteries arise from the aorta, below the renal vessels. The left ovarian vein empties into the left renal vein and the right ovarian vein into the inferior vena cava. The ovary's primary lymphatic drainage is to the upper aortic and caval lymph nodes,[9] which may be an important site of occult metastasis even in apparently early stages of ovarian cancer.[10]

The nerve supply to the ovary comes from the sympathetic plexus, so a patient with an ovarian tumor may complain of vague mid-abdominal discomfort rather than pelvic pain. Pelvic pain usually reflects pressure on contiguous organs from direct extension or extrinsic pressure.

Histologic Classification of Ovarian Neoplasms

The classification of ovarian tumors in this chapter is that adopted by the World Health Organization (WHO) (Table 11-1). The epithelial tumors derive from the coelomic (germinal) epithelium. In women of all ages epithelial malignancies account for 75–90% of all ovarian cancer, whereas germ cell tumors and stromal tumors comprise 15–20% and 5–10%, respectively. However, in children under 18, germ cell malignancies account for 63–74% of malignant tumors, whereas stromal tumors represent 17–20% and epithelial cancers 4.5–12.5%.[3,5,11–13]

The majority of ovarian tumors found in children or adolescents are benign. In fact, many series have found the overall malignancy rate to be only 15–32%.[11,14,15] One notable exception, however, is the large series from The Armed Forces Institute of Pathology in which 200 of 353 neoplasms were malignant.[16]

Symptomatology of Ovarian Tumors

The diagnosis of ovarian neoplasia is hindered by the abdominal and pelvic location of the ovary and the relatively asymptomatic nature of the disease. Even in the advanced stages of ovarian carcinoma, the patient may relate a history of only vague gastrointestinal symptoms such as early satiety, intermittent bloating, altered intestinal motility, dyspepsia, or nondescript abdominal discomfort. Pressure upon adjacent organs sometimes promotes symptoms such as constipation and frequent urination. However, even in the adult patient in whom this constellation of symptoms should prompt an evaluation for ovarian cancer, the diagnosis frequently is not made until the disease is in an advanced stage.[3]

In women under 18, the diagnosis of ovarian carcinoma is often delayed because the rarity of the lesion makes it an unlikely possibility, and a pelvic examination may be physically and psychologically uncomfortable for the young patient. Therefore, if a reliable gynecologic examination cannot be done because of anxiety or discomfort, an examination under anesthesia or by laparoscopy should be done to evaluate the ovaries once the diagnosis of ovarian carcinoma has been entertained. Occasionally an ovarian tumor presents with acute abdominal symptoms from infarction as a result of gonadal torsion. Rapid growth and/or hemorrhage into the

Table 11-1. Histoligic Classification of Ovarian Tumors.

I. Common "epithelial" tumors
  A. Serous tumors
    1. Benign
      a. Cystadenoma and papillary cystadenoma
      b. Surface papilloma
      c. Adenofibroma and cystadenofibroma
    2. Of borderline malignancy (carcinomas of low malignant potential)
      a. Cystadenoma and papillary cystadenoma
      b. Surface papilloma
      c. Adenofibroma and cystadenofibroma
    3. Malignant
      a. Adenocarcinoma, papillary adenocarcinoma, and papillary cystadenocarcinoma
      b. Surface papillary carcinoma
      c. Malignant adenofibroma and cystadenofibroma
  B. Mucinous tumors
    1. Benign
      a. Cystadenoma
      b. Adenofibroma and cystadenofibroma
    2. Of borderline malignancy (carcinomas of low malignant potential)
      a. Cystadenoma
      b. Adenofibroma and cystadenofibroma
    3. Malignant
      a. Adenocarcinoma and cystadenocarcinoma
      b. Malignant adenofibroma and cystadenofibroma
  C. Endometrioid tumors
    1. Benign
      a. Adenoma and cystadenoma
      b. Adenofibroma and cystadenofibroma
    2. Of borderline malignancy (carcinomas of low malignant potential)
      a. Adenoma and cystadenoma
      b. Adenofibroma and cystadenofibroma
    3. Malignant
      a. Carcinoma
        i. Adenocarcinoma
        ii. Adenoacanthoma
        iii. Malignant adenofibroma and cystadenofibroma
      b. Endometrioid stromal sarcomas
      c. Mesodermal (müllerian) mixed tumors, homologous and heterologous
  D. Clear cell (mesonephroid) tumors
    1. Benign: adenofibroma
    2. Of borderline malignancy (carcinomas of low malignant potential)
    3. Malignant: carcinoma and adenocarcinoma
  E. Brenner tumors
    1. Benign
    2. Of borderline malignancy (proliferating)
    3. Malignant
  F. Mixed epithelial tumors
    1. Benign
    2. Of borderline malignancy
    3. Malignant
  G. Undifferentiated carcinoma
  H. Unclassified epithelial tumors
II. Sex cord stromal tumors
  A. Granulosa-stromal cell tumors
    1. Granulosa cell tumor
    2. Tumors in the thecoma-fibroma group
      a. Thecoma
      b. Fibroma
      c. Unclassified
  B. Androblastomas; Sertoli-Leydig cell tumors
    1. Well differentiated
      a. Tubular androblastoma; Sertoli cell tumors (tubular adenoma of Pick)
      b. Tubular androblastoma with lipid storage; Sertoli cell tumor with lipid storage (*folliculome lipidique* of Lecene)
      c. Sertoli-Leydig cell tumor (tubular adenoma with Leydig cells)
      d. Leydig cell tumor; hilus cell tumor
    2. Of intermediate differentiation
    3. Poorly differentiated (sarcomatoid)
    4. With heterologous elements
  C. Gynandroblastoma
  D. Unclassified
III. Lipid (lipoid) cell tumors
IV. Germ cell tumors
  A. Dysgerminoma
  B. Endodermal sinus tumor
  C. Embryonal carcinoma
  D. Polyembryoma
  E. Choriocarcinoma
  F. Teratomas
    1. Immature
    2. Mature
      a. Solid
      b. Cystic
        i. Dermoid cyst (mature cystic teratoma)
        ii. Dermoid cyst with malignant transformation
    3. Monodermal and highly specialized
      a. Struma ovarii
      b. Carcinoid
      c. Struma ovarii and carcinoid
      d. Others
  G. Mixed forms
V. Gonadoblastoma
  A. Pure
  B. Mixed with dysgerminoma or other forms of germ cell tumor
VI. Soft tissue tumors not specific to ovary
VII. Unclassified tumors
VIII. Secondary (metastatic) tumors
IX. Tumorlike conditions
  A. Pregnancy luteoma
  B. Hyperplasia of ovarian stroma and hyperthecosis
  C. Massive edema
  D. Solitary follicle cyst and corpus luteum cyst
  E. Multiple follicle cysts (polycystic ovaries)
  F. Multiple luteinized follicle cysts and/or corpora lutea
  G. Endometriosis
  H. Surface-epithelial inclusion cysts (germinal inclusion cysts)
  I. Simple cysts
  J. Inflammatory lesions
  K. Parovarian cysts

From Scully.[5]

tumor also may cause pain. The clinical appearance of excessive estrogen or androgen should alert the physician to possible ovarian pathology.[3,13]

The Adnexal Mass

When a mass is found in the region of the adnexal organs (the ovaries and fallopian tubes) a plan must be established to reach a diagnosis. This plan must protect the patient against a delay in diagnosis, yet also must be tempered with a rational conservativeness since most adnexal masses are nonneoplastic and may undergo spontaneous resolution.[17]

The physical examination and menstrual status of the patient guide the decision for operative intervention. The only pelvic mass that should be temporarily observed in the female pelvis is the unilateral, cystic, mobile, nontender adnexal mass which is less than 5 cm in largest diameter.[18,19] This mass is usually a physiologic follicular or corpus luteal cyst of the ovary. However, such a cyst can be observed only in the appropriate clinical setting. For example, neither a prepubertal child nor a postmenarchal patient taking oral contraceptives should develop a physiologic cyst. Specific indications for immediate removal of an adnexal mass in a child or adolescent are (1) an adnexal mass before puberty; (2) an adnexal mass in a patient who takes oral contraceptives; (3) any solid, fixed, or tender mass; or (4) a mass, cystic or solid, greater than 6 cm in diameter.[3,18,19]

The use of hormones in the differential diagnosis of the adnexal mass that does not meet the criteria for immediate laparotomy has proven quite effective in eliminating the functional ovarian cyst without laparotomy.[17] The functional cyst will spontaneously resolve, while oral contraceptives prevent the occurrence of a second physiologic cyst by suppressing the pituitary-gonadal axis. This suppression avoids confusing a second, unrelated cyst with a cystic lesion that has failed to resolve. In a series from Los Angeles County in which patients who presented with a solitary, cystic, mobile adnexal mass were given hormonal therapy preoperatively for 6 weeks, 205 of 286 patients (71.6%) had regression in the adnexal lesion and did not require surgery. Of the 81 patients explored, none had a physiologic cyst, while 34.5% had an endometrioma, 50.6% had benign ovarian neoplasms, 8.6% had either tubal pathology or parovarian cysts, and 6.2%—including one girl who was 16—had ovarian malignancies.[17]

The physical examination of an adnexal mass is at times inconclusive, and the clinician may seek further evaluation prior to establishing a course of action. Although a roentgenogram of the abdomen occasionally may be beneficial, if calcifications or the semilucent nature of a dermoid cyst are appreciated, these findings cannot guarantee benignity becaue dysgerminomas, gonadoblastomas, and serocystadenocarcinomas can calcify or occur adjacent to an otherwise benign tumor.[13] Ultrasonography can be extremely useful in that it may better define the cystic or solid nature of the mass.[13,20] A purely cystic lesion satisfies the criteria for a functional cyst, whereas a cystic lesion with internal echoes or a solid lesion warrants immediate laparotomy.

If the adnexal mass appears malignant on examination (e.g., the mass is fixed, hard, multinodular, or associated with ascites), a more thorough radiographic evaluation is necessary preoperatively to study adjacent organs for either an occult primary or metastases. Chest roentgenograms and an intravenous pyelogram are essential; a barium study of either the upper or lower intestine or a computerized tomogram is determined on an individual basis. Venograms, arteriograms, and lymphangiograms may be necessary on rare occasions.

Surgical Approach to the Adnexal Mass in Childhood and Adolescence

When an exploratory laparotomy is conducted for an adnexal mass, a Pfannenstiel incision (low transverse) is appropriate only when there is an unequivocal diagnosis of benign disease. For example, such a patient might have had a dermoid documented by roentgenogram or endometriosis confirmed by laparoscopy. When the mass exceeds the size of the transverse incision, however, or when malignancy is suspected, the operating surgeon must use a vertical incision. If a wrong decision has been made initially and a malignant ovary found through a Pfannenstiel incision, the incision

must be converted to a vertical opening to allow for adequate visualization and access to the upper abdomen and retroperitoneal lymph nodes.[21,22]

Upon opening the abdominal cavity, the operating surgeon should collect ascites, or if none is present, wash the pelvis and pericolic gutters with normal saline and submit each specimen separately for cytologic review. The abdomen should be thoroughly evaluated for evidence of malignancy distant from the ovary or for a primary tumor that might have metastasized to the ovary. After evaluating the abdomen, the initial approach to the pelvic organs should include a thorough inspection to determine the tumor's origin, sites of attachment, or evidence of extraovarian spread and careful inspection of the contralateral adnexa. If extraovarian disease is not identified and malignancy not suspected, either an ovarian cystectomy or oophorectomy should be done. In general, the surgical approach in this age group should be conservational until a malignancy is diagnosed. If a diagnosis cannot be made by frozen section, then it seems proper to end the operative procedure until the permanent pathology can be studied and thoroughly reviewed. Reexploration for surgical staging and complete expiration of the reproductive organs may be necessary subsequently but appears preferable to what may be unnecessary castration.[10,18,19,21,22]

If a malignancy is diagnosed by frozen section evaluation, then the ipsilateral ovary and tube should be evaluated and probably biopsied, and a careful search made for extraovarian spread. Since most tumors that occur in women under 20 are malignant germ cell tumors that have a relatively low incidence of bilaterality, hysterectomy and contralateral oophorectomy may not be necessary. If there is obvious malignant involvement of the contralateral ovary, it should be excised after histologic confirmation. Because it is not uncommon to find a benign teratoma in the ovary opposite to a germ cell malignancy, extirpation of the contralateral ovary should be avoided until a malignancy is unequivocally documented.[5,13,18,19]

When extraovarian disease is not obvious but ovarian cancer is confirmed, biopsies in search of occult malignant spread should be obtained from the parietal peritoneal surfaces in the pelvic, pericolic, and subdiaphragmatic spaces.[10,21,22] The omentum should be biopsied and an infracolic omentectomy performed in the absence of overt tumor involvement. A total omentectomy usually is required for more advanced cases. Any suspected malignant deposits on the visceral surfaces should be biopsied and/or excised. In this age group the exact incidence of lymph node metastasis in ovarian cancer is uncertain, so it is necessary to excise the lymph nodes immediately adjacent to the aorta and vena cava.

In patients with metastatic carcinoma, aggressive surgical resection of all metastatic disease improves tumor responsiveness to chemotherapy and prolongs survival.[13,21-24] This favorable result of aggressive tumor reductive surgery is believed to be from the excision of masses of nonproliferating but potentially clonagenic cells that are exposed to sublethal concentrations of chemotherapeutic agents because they reside within partially necrotic and devascularized tumors.[23,25] In addition, the growth behavior in these tumor nodules may be altered following tumor reductive surgery, resulting in an increase in the percentage of proliferating cells, which makes the tumor more vulnerable to chemotherapy. Other changes after tumor reduction may favorably influence the immunologic responses of the host.[23,25] The value of aggressive surgical resection in nonepithelial ovarian malignancy is less well established because of the paucity of cases with advanced stage malignancy. However, several authors report poorer responses in patients with advanced unresectable germ cell and stromal tumors than in those with a similar disease status in whom the cancer had been radically resected prior to chemotherapy.[26-31]

The Surgical Staging of Ovarian Cancer

Ovarian cancer is the only gynecologic tumor that is completely staged by surgical exploration. It is therefore necessary to become familiar with the staging system adopted by the International Federation of Gynecologists and Obstetricians (Table 11-2).

Table 11-2. Stage Grouping for Primary Carcinoma of the Ovary in Common Epithelial Ovarian Cancer.

Stage I	
	Growth limited to the ovaries
IA	Growth limited to *one* ovary; no ascites
	1. No tumor on the external surface; capsule intact
	2. Tumor present on the external surface and/or capsule ruptured
IB	Growth limited to *both* ovaries; no ascites
	1. No tumor on the external surface; capsule intact
	2. Tumor present on the external surface and/or capsule(s) ruptured
IC	Tumor either stage IA or IB, but with ascites[a] or positive peritoneal washings
Stage II	
	Growth involving one or both ovaries with pelvic extension
IIA	Extension and/or metastases to the uterus and/or tubes
IIB	Extension to other pelvic tissues
IIC	Tumor either stage IIA or IIB, but with ascites[a] or positive peritoneal washings
Stage III	
	Growth involving one or both ovaries with intraperitoneal metastases outside the pelvis and/or positive retroperitoneal nodes; tumor limited to the true pelvis, with histologically proven malignant extension to small bowel or omentum
Stage IV	
	Growth involving one or both ovaries with distant metastases; if pleural effusion is present, there must be positive cytology to allot a case to stage IV; parenchymal liver metastases are classified in stage IV
Special Category	
	Unexplored cases which are thought to be ovarian carcinoma

[a]Ascites is peritoneal effusion which in the opinion of the surgeon is pathologic and/or clearly exceeds normal amounts.
From Young RC, et al.[10]

Germ Cell Tumors of the Ovary

Germ cell tumors (GCT) of the ovary arise from the primitive germ cells of the gonad. The origin has been derived from observing the common histogenesis of these tumors, the concurrence of histologically different tumor elements within the same neoplasms, the presence of similar tumors in extragonadal locations along the primitive germ cell's line of migration from the yolk sac to the gonadal ridge, and the similarity between various tumors of the ovary and testis.[32] As a group, GCT represent 15–20% of ovarian tumors. They are much more common in the younger cohorts, however. Sixty percent of ovarian tumors in women under 20 are germ cell neoplasms. Although most germ cell tumors (approximately 95%) are benign cystic or mature teratomas, the discussion in this chapter deals with only malignant neoplasms.[5,32]

Despite the rarity of malignant GCT, different histologic types are well recognized and distinguishable by clinical and biochemical association. The dysgerminoma is a malignant tumor derived from primordial germ cells prior to any differentiation. Other germ cell tumors have been subclassified depending upon neoplastic differentiation, either toward embryonal structures (teratomas, mature and immature) or extraembryonal structures (endodermal sinus tumors, choriocarcinoma, embryonal carcinoma, and polyembryoma). Mixed germ cell tumors that have more than one histologic type present represent approximately 8% of germ cell malignancies.[5,32,33]

Dysgerminoma

Although dysgerminoma represents only 3–5% of all malignant ovarian tumors it is the most common ovarian malignancy in the adolescent female. Fewer than 10% occur prior to menarche, yet 45% occur before age 20. Although dysgerminoma occasionally is found during pregnancy, the occurrence reflects the frequency of the tumor in this age group and does not signify any risk factors from pregnancy itself.[5,32,33]

Dysgerminoma is composed of primordial germ cells that are sexually indifferent and hormonally inert. Whereas 15–20% of dysgerminomas may be mixed with other malignant germ cell elements, this current discussion is limited to the pure dysgerminoma because of the marked biologic difference between the pure and mixed forms. For example, Gordon et al documented 83% and 74% 5- and 10-year survivals for all patients with pure dysgerminoma as opposed to 31% and 24% 5- and 10-year survivals for dysgerminoma mixed with other germ cell elements.[34] Consequently, any discussion of treatment for dysgerminoma requires sufficient histologic evaluation of the tumor to exclude more aggressive germ cell elements. Some authors have suggested that germ cell tumors should be evaluated with one microscopic slide per centimeter of tumor, concen-

trating on the solid and hemorrhagic tumor areas.[5,32,33]

The symptoms associated with dysgerminoma usually are vague, nonspecific abdominal and pelvic discomfort. Dysgerminoma, with or without a concomitant gonadoblastoma, occasionally may occur in patients with dysgenetic gonads with either pseudohermaphroditism or incomplete genital development.[5,33,35] On occasion, pure dysgerminoma is associated with a positive pregnancy test resulting from the secretion of HCG from multinucleated syncytiotrophoblastic-like cells.[5,32,33]

Dysgerminoma spreads by either perforation of the ovarian capsule and direct extension to other pelvic structures or by lymphatic embolization, primarily to the periaortic lymph nodes.[33,34] Bilateral ovarian involvement occurs in 10–15%, which is more common than with any other GCT.[32,34] Most patients (55–75%) are stage I upon diagnosis, approximately 10% stage II, 10% stage III, and 5% either stage IV or stage unknown.[36,37]

The treatment of pure dysgerminoma depends upon the stage. The initial treatment is surgical extirpation of the tumor with thorough surgical staging. When postoperative therapy is indicated, radiation therapy is preferred. In the multiparous patient or someone with bilateral ovarian involvement, a total abdominal hysterectomy and bilateral salpingo-oophorectomy is the best surgical procedure. However, several authors encourage a conservative surgical approach in the nulliparous patient and recommended only a unilateral salpingo-oophorectomy in those with stage IA disease.[3,18,34,38,39] The contralateral ovary should be biopsied, however, due to the relative frequency of occult bilateral involvement.

The recurrence rate among patients treated conservatively ranges from 17 to 22%, compared to 10% for those receiving more aggressive initial surgical therapy.[34,39,40] However, due to a 50–60% salvage rate in patients developing recurrence subsequently treated with radiation therapy, the 5- and 10-year survival for this tumor still approaches 90%, regardless of whether the initial surgery included a unilateral or bilateral salpino-oophorectomy. Since 80% of patients treated conservatively maintained reproductive function, this outline of treatment still is encouraged because reproductive capacity is preserved in many, yet the overall 5-year survival rates are not compromised.

In patients with greater than stage IA dysgerminoma, a total abdominal hysterectomy and bilateral salpingo-oophorectomy should be done in addition to surgical debulking. Postoperative radiation therapy is useful in treating unresectable tumor and metastases. Since dysgerminoma is very radiosensitive, 2500–3500 rads delivered in 2.5 to 4 weeks usually is tumoricidal.[38,39]

Five-year survival for dysgerminoma devoid of any other germ cell elements ranges from 80 to 90%.[34,36,39] Even advanced stage tumors can be treated successfully with aggressive surgical resection and radiotherapy.[41]

Tumor recurrences frequently are identified within the initial 24 months following treatment. Recurrence sites are the abdomen, pelvis, and periaortic and supraclavicular nodes. Radiation therapy frequently is successful in managing recurrence including, if necessary, reirradiation of body regions.[34,39] Although chemotherapy is less often used, combinations of vincristine, actinomycin, and cyclophosphamide or vinblastine, bleomycin, and cis-platinum appear active.[42,43]

Endodermal Sinus Tumors

The endodermal sinus tumor (EST) is the second most common malignant germ cell tumor (22%). The tumor occurs after the malignant degeneration of the multipotential germ cell toward extraembryonal structures, forming a histologic pattern reminiscent of the endodermal sinuses of the yolk sac. EST may occur in a pure form or mixed with other germ cell elements. When coexisting with other malignant germ cell elements, it frequently is the most malignant and metastasizing component.[32,33]

The median age for patients with EST is 16 to 19, with an age range from 13 months to 57 years. Seventy-seven percent of the patients are white, 18% are black; 60% are postmenarchal, 40% of whom are parous. Seventy-seven percent of patients present with pain, 74% with an abdominal or pelvic mass, and 24% have fever. In 66%, symptoms began less than 2 weeks prior to seeking medical help. Approximately

71% of the tumors are stage I (16% with ascites), 6% stage II, and 23% stage III. Most series have an occasional stage IV patient. Stage IB disease is rare, allowing for conservation of the contralateral gonad and uterus in stage I patients. Five percent may have a dermoid in the contralateral gonad.[5,32,33,44] Pure EST is hormonally inert. However, tumor production of α-fetoprotein has been demonstrated by immunoperoxidase techniques. Serum levels of α-fetoprotein correlate well with residual cancer volume, and as such, α-fetoprotein is a reliable tumor marker for both diagnosis and for monitoring the course of subclinical disease during chemotherapy.[45–47]

The prognosis for EST has been poor. Without modern adjuvant chemotherapy, 85% of apparent stage I disease recurs, with death occurring within 24 months of diagnosis.[5,32,44,48] Overall 3- and 5-year survival rates have been reported at 9–13%.[44,49] There are no universally recognized histologic or clinical characteristics that portend a good prognosis.

In stage I disease survival does not improve by removing the uninvolved uterus and contralateral ovary. In fact, because bilateral ovarian involvement is quite rate, unilateral salpingo-oophorectomy often is encouraged except in institutions that recommend postoperative pelvic radiation.[44,48,49] Aggressive tumor reductive surgery for advanced stage malignancy may be beneficial.[27–30]

Patients in many institutions now receive postoperative multiagent chemotherapy, and the previously dismal prognosis is improving. Neither the optimal chemotherapy regimen nor the duration of treatment is known. Vincristine, dactinomycin, and cyclophosphamide (VAC) have been given for as long as 2 years with a 72–75% long-term survival.[28,50] Recently, another regimen consisting of vinblastine, bleomycin, and cis-platinum (VBP) has been promoted and appears quite active.[29,43,50] Other regimens, including the Duke protocol of methotrexate, dactinomycin, and chlorambucil (MAC), which is given only for three courses, also have been favorably reported.[26,30]

The role of radiation therapy in EST is unknown. Although postoperative radiation therapy alone has been unable to control EST, several authors recommend that postoperative radiation therapy be given in combination with chemotherapy to enhance local responses in both the pelvic and periaortic areas.[30,48–51] However, in a disease that frequently requires intensive chemotherapy, any sacrifice of bone marrow tolerance by pelvic or abdominal radiation therapy eventually may limit the patient's tolerance for systemic treatment. Moreover, routine postoperative radiation therapy to the pelvis eliminates conservative pelvic surgery for the preservation of reproductive function.

Patients with EST should be monitored during chemotherapy with serum α-fetoprotein (AFP) levels. When serum AFP is undetectable following chemotherapy, it is advisable for that patient to undergo a laparotomy to confirm the disease-free status.[28,29,50] At present, a second-look operation still is considered necessary since the tumor burden may be sufficiently low to prevent detection of serum AFP despite the presence of viable tumor, or because the initial tumor may have been mixed with other germ cell elements that are not protein secreting.

Immature Teratoma

Immature teratoma (IM) accounts for 15% of malignant GCT. The tumor is somewhat more frequent in children under 15. IM is hormonally inert and symptoms relate only to a rapidly growing abdominal mass. The neoplasm contains variable amounts of immature tissue derived from one or all of the three germ cell layers. The tumors usually are large (medium size, 18 cm), unilateral, and frequently contain mature elements such as hair, bone, and cartilage. This tumor should not be confused with an extremely common dermoid tumor with its benign germ cell elements, or the dermoid which has undergone malignant degeneration of one histologic element.[5,33,52–55]

The immaturity of the tissue indicates the metastatic capability of this tumor, and this malignant potential is reflected in the grading system that has been developed. Since immature neuroepithelium is the most common element usually identified in an immature teratoma, some pathologists concentrate on this particular component of the histology

when assigning grades, whereas others evaluate the amount of all embryonal tissue present. Grade 0 is assigned to tumors that are composed totally of well-differentiated tissue. This tumor is benign and does not metastasize. Grade 1 tumors contain a rare and small focus of embryonal tissue. Consequently, these tumors have a substantial amount of mature tissue and may be confused with a dermoid. Grade 2 tumors have a moderate quantity of embryonal tissue, while grade 3 tumors are made up mostly of embryonal tissue.[5,52–55]

Norris has demonstrated that the grade of the tumor predicts metastatic spread, whereas the grade of the metastasis determines survival. In his series of 58 cases, most stage IA tumors were either grade 1 or 2, whereas most patients with stage III disease had either grade 2 or 3 neoplasms. The prognostic relationship of grade is evident in stage IA patients—100% of patients with grade 1 tumors survived, but only 70% of patients with grade 2, and 33% of patients with grade 3 neoplasms survived. When all stages were considered collectively, survival for grades 1, 2, and 3 were 82, 63, and 30%, respectively.[55]

The treatment of immature teratoma depends upon the stage, the histologic grade of the primary tumor, and if present, the grade of the metastatic lesions. Stage I neoplasms are almost exclusively unilateral and therefore the initial surgical treatment can be a unilateral salpingo-oophorectomy. Since 5% of patients may have a benign dermoid in the contralateral ovary, a contralateral lesion should be biopsied before excision of the adnexa. Stage IA , grade 0 and 1 neoplasms do not appear to require postoperative therapy. However, because recurrence rates in untreated patients with stage IA, grade 2 or 3 tumors appear in excess of 45%, postoperative chemotherapy is indicated in all patients with this stage or more advanced disease. Chemotherapy also may be indicated when a tumor has ruptured during surgical removal.[53,55]

Combined chemotherapy has improved significantly the long-term outlook for this disease. The most common regimens have been either VAC or MAC. Prior to combination chemotherapy the mortality rate for this tumor approached 90 to 100%. However, the current literature indicates a survivorship of greater than 75%. The duration of chemotherapy still is unsettled, ranging from 3 to 24 months at various institutions. A second-look operation is highly recommended. Retroconversion of malignant metastasis to mature, grade 0 implants at second-look laparotomy has been identified in isolated cases. These lesions appear benign and most authorities do not believe that they require further chemotherapy, although Curry et al[53] have found one case that was progressing.[4,28,30,56,56a,57]

A consensus of the literature does not support the use of radiation therapy for this disease.

Embryonal Carcinoma

Embryonal carcinoma is a rare malignant germ cell tumor of the ovary (4–5%), with a unique clinical constellation and distinctive histologic features similar to the more common embryonal carcinoma of the testis. In the 15 patients reported by Kurman and Norris,[56a] the median age was 14 years with a range from 5 to 28. In addition to the symptoms of abdominal enlargement and pains similar to all ovarian germ cell tumors, 60% had associated hormonal manifestation, which included isosexual precocious puberty in seven (42%), mild hirsutism and amenorrhea in one, and either oligomenorrhea or menstrual irregularities in five. All tumors appear to synthesize human chorionic gonadotropin, and most (70%) synthesize α-fetoprotein.[57a] Consequently, pregnancy tests frequently are positive in this group. Both AFP and HCG are useful tumor markers. Most patients present with stage I disease (60%), and initial surgery can be limited to a unilateral salpingo-oophorectomy. Kurman recommends a wedge biopsy of the contralateral ovary, however. Patients with stage II or III disease require tumor reductive surgery. Although the number of published cases is small, radiation therapy does not appear effective. Postoperative chemotherapy should include one of the multiagent regimens (VAC, MAC, or VBP) effective against other germ cell tumors. The actuarial survival is 39% for all stages and 50% for stage I patients.[5,33,56,56a,57]

Polyembryoma

This is an extremely rare tumor. Most reported cases are those where the polyembry-

oma pattern has been intermixed with other germ cell elements. Histologically, the tumor consists of embryoid bodies that attempt to replicate the early embryo cell mass. The tumor has been noted to secrete HCG and AFP. Because so few cases have been reported, it is best to treat this tumor similar to other malignant germ cell tumors.[5,33,58]

Choriocarcinoma

Pure nongestational choriocarcinoma of the ovary is very rare, although choriocarcinoma frequently is mixed with other malignant germ cell tumors. Pure choriocarcinoma is seen most frequently in children and young adults, but this age distribution may be biased by the difficulty in distinguishing between the gestational and nongestational types in women who are sexually active. Due to the secretion of HCG, isosexual precocious puberty is common in children with this tumor. HCG is an effective tumor marker.

Nongestational choriocarcinoma of the ovary is a very malignant tumor. The operative and postoperative management of this tumor should be consistent with treatment of other malignant GCT. Chemotherapy regimens containing methotrexate and actinomycin have been advocated because of prior success in treating gestational choriocarcinoma. In general, however, nongestational choriocarcinoma is less responsive to chemotherapy than its gestational counterpart, although long-term successes have been reported.[5,33,59]

Mixed Germ Cell Tumors

Mixed germ cell tumors contain more than one germ cell type and represent 8% of all malignant GCT. In the 30 patients studied by Kurman and Norris, dysgerminoma was idenified in 80%, endodermal sinus tumor in 70%, immature teratoma in 53%, choriocarcinoma in 20%, and embryonal carcinoma in 16%.[60] Consequently, patients not only present with a common symptomatology such as enlarging abdominal mass or abdominal pain, but some also have precocious puberty, menstrual alterations, or a positive pregnancy test. Serum HCG and AFP levels frequently are elevated, and can be valuable tumor markers. More than 60% of patients present with stage I tumor, and survival for stage I has ranged from 23 to 50%. For patients with stage I disease, prognosis depends upon the tumor size and composition. In one study, all patients whose tumors measured less than 10 cm in diameter and contained less than 33% of the notoriously more malignant element (e.g., EST, choriocarcinoma, or grade 3 IM) survived, as opposed to no survivors when the opposite characteristics were identified. According to these authors, the mere presence of these more malignant components within the mixed GCT was not as significant clinically as their quantity.[60]

Most stage I patients have only unilateral ovarian involvement; therefore unilateral salpingo-oophorectomy has been recommended for women who desire children in the future. However, since dysgerminoma is a frequent constituent of the tumor, wedge biopsy of the contralateral ovary has been recommended.[5,33,60-62]

In most series, surgical therapy alone appears to be inadequate. Jimerson and Woodruff reported that nine of 11 patients with stage I disease died of their tumor following surgical extirpation alone.[61] Similarly, in another series all eight patients who were treated with surgery alone had recurrences.[62] In contrast, however, Kurman and Norris reported seven survivors of 13 patients treated only with surgery,[60] and they recommend adjunctive postoperative chemotherapy in only those with adverse prognostic features such as a tumor larger than 10 cm or a tumor in which more than one-third is comprised of EST, choriocarcinoma, or grade 3 IM.

The chemotherapy recommended for these tumors is the same as that mentioned for EST, IM, and embryonal tumors. The role of radiation therapy is unknown.[4,28,30,60-62]

Gonadoblastoma

A gonadoblastoma is a tumor that almost exclusively arises in patients with sex chromosome abnormalities and gonadal maldevelopment. This tumor consists of germ cells histologically similar to those seen in dysgerminoma but lacking invasive properties and cells of sex cord origin.[32,63] The age range is from 6 to 38. Eighty percent of tumors are in phenotypic women and 20% in phenotypic

males who may show cryptorchidism, hypospadias, or rudimentary internal female reproductive organs. Both estrogens and androgens have been synthesized by these tumors. Consequently, phenotypic females may demonstrate virilization, isosexual precocity, amenorrhea (usually primary but occasionally secondary), and breast development.[32,63–71]

The gonadoblastoma may be clinically diagnosed in the intersex patient by palpating an abdominal mass or identifying calcified masses in the lower abdomen by roentgenogram. However, 25% of tumors have been microscopic and diagnosed only after the surgical removal of an abnormal gonad. There is a 33% incidence of bilateral gonadal involvement.[32,63]

Pure gonadoblastoma is biologically benign and has been described as a germ cell tumor in situ because it does not tend to invade contiguous organs or metastasize. However, 50% of gonadoblastomas may have associated dysgerminomas, and 20% have been associated with other malignant germ cell tumors. Therefore, although surgical removal of the ovaries is the only required treatment in patients with pure gonadoblastoma, those who have other germ cell elements intermixed with this tumor must have therapy that is directed toward the most malignant component.[32,35,66]

Karyotype investigation in phenotypic females with gonadoblastoma reveals a 46,XY pattern in 50% and a 45,X/46,XY pattern in 25%. Overall, 90% of patients with gonadoblastoma are sex chromatin negative.[35,63] The estimated risk for an intersex patient with a Y-chromosome developing either a gonadoblastoma or other malignant germ cell tumor is approximately 15 to 25%. Gonadoblastomas have been identified in true hermaphrodites. Schellhas[35] has found that dysgenetic gonads without a Y-chromosome (e.g., 45,X,45,XO/46,XX) are at very low risk for developing a tumor.[63,64,67]

Because of the potential for either gonadoblastoma or other malignant germ cell tumor development, most authorities recommend that the Y-bearing dysgenetic gonad be removed.[35,63,67,69,70] Bilateral salpingo-oophorectomy is the indicated procedure since there is a 33% incidence of bilaterality, almost universal infertility, and the associated hormone production that frequently can virilize a phenotypic female. Hysterectomy is not always indicated because some clinicians foresee a psychologic advantage to exogenously controlled menstruation. Patients with more malignant germ cell tumors obviously should have both the operative and postoperative therapy tailored for their type and stage of ovarian tumor.

Manuel et al studied the age gonadal tumors occurred in intersex patients with Y-chromosomes to determine when gonadectomy should be done.[67] In patients with gonadal dysgenesis, asymmetric gonadal differentiation, or male hermaphroditism, the rate of tumor occurrences rises sharply at puberty. Thus, it is recommended that these patients' ovaries be removed prior to puberty. However, in those with testicular feminization, the risk of an ovarian neoplasm is only 4% until age 30, so it has been suggested that if one is willing to assume this risk the gonads should remain until the patient has been allowed to spontaneously feminize.[35,63,70]

Talerman has described several mixed germ cell–sex cord stromal tumors in normal 46,XX children, some of whom have developed isosexual precocious puberty.[68] This tumor appears clinically distinct from the gonadoblastoma, although it resembles the latter histologically. Bilateral salpingo-oophorectomy should be avoided since this tumor does not appear to be associated with other malignant GCT and occurs in a genetically normal person with normal gonads. This tumor appears to have an extremely low malignant potential, if any at all. Several patients have been followed from 2 to 9 years following unilateral salpingo-oophorectomy and have had no recurrence. Obviously, the number of cases reported is extremely small. Therefore, each patient must be evaluated thoroughly prior to assigning her to such a category.[68]

Sex Cord Stromal Tumors

The sex cord stromal tumors (SCST) represent 5–10% of all ovarian neoplasms and approximately 12% of ovarian tumors in childhood and adolescence. In this age group, the SCST are much less common than germ cell tumors but occur almost as frequently as the epithelial carcinomas.[11,71,72] The frequency of SCST ap-

pears related to age. In one series of 648 ovarian tumors in children, 48% of ovarian neoplasms in those younger than age 4 were SCST, whereas SCST represented only 30% in children 5 to 9, 8% between ages 10 to 14, and 16% for those 15 to 17.[72] Seventy-five percent of the prepubertal SCST are hormonally active and lead to precocious puberty, but this is an extraordinarily uncommon etiology for precocious puberty. Hormone activity is less pronounced clinically after puberty but may manifest by menstrual irregularity, breast stimulation, and hypermenorrhea.[5,72,73]

The SCST are composed of a variety of sex cord and stromal elements and may differentiate toward ovarian tissue as granulosa or thecal tumors. SCST may differentiate toward testicular tissue as a Sertoli-Leydig tumor (arrhenoblastoma).[73]

Granulosa Cell Tumors

Granulosa cell tumors are the most common of the SCST and usually are associated with estrogen production, although an occasional tumor has been androgenic.[74,75] The tumor generally is described as a low grade malignancy because most tumors are stage I at presentation, 10-year survival is nearly 80%, and recurrences are common more than 10 years following initial treatment.[5,76]

Several factors are related to prognosis. The stage is most significant with a 10-year survival rate for patients who have stage I disease ranging from 85 to 95%, whereas those patients with more advanced stages are reported to have a 26 to 49% chance of survival.[73,76–78] Bjorkholm reported a decrease in the 25-year survival from 86% for intact tumor to 60% for tumors ruptured either spontaneously or during surgical removal.[79] The 5-year survival also has been reported to decrease from a range of 73 to 100% for tumors less than 5 cm in diameter to 34 to 53% for tumors larger than 15 cm.[79,80] The influence of histologic type on survival is uncertain, although some report a worsened prognosis with poorly differentiated or sarcomatoid pattern.[73]

Only 10% of granulosa cell tumors occur before the age of 20 years and half of these occur before puberty. Although a clinical curiosity, the tumor is an infrequent cause of isosexual precocious puberty. Clinically, 15% of patients present with hemoperitoneum as a result of tumor rupture. Five percent have bilateral ovarian involvement.[73,81,82] Because of the low malignant potential of this tumor, many oncologists recommend a unilateral salpingo-oophorectomy when the tumor is confined to one ovary and future reproduction is desired. However, because of the risk of delayed local recurrence, hysterectomy and excision of the contralateral ovary are recommended for those who are through with childbearing, even though no obvious malignancy persists.[77,78] Prior to conservative surgery, however, an endometrial biopsy should be done to exclude any synchronous endometrial carcinoma resulting from the granulosa cell tumor's chronic estrogen secretion.[74,77] Moreover, conservative surgery may carry some risk; several authors have observed a higher local recurrence rate in women treated with unilateral salpingo-oophorectomy than in those who have had a total abdominal hysterectomy and bilateral salpingo-oophorectomy as the initial surgical treatment.[77,78]

Patients with advanced stage or recurrent granulosa cell carcinoma have been treated with chemotherapy and radiation. The most effective chemotherapy regimen is unknown, but multiagent or doxorubicin-containing regimens are preferred.[83–85] However, due to the limited number of metastatic and recurrent cases reported, specific recommendations cannot be made regarding radiotherapy or precise chemotherapy regimens.

Juvenile Granulosa Cell Tumors

Scully has called attention to a clinically and histologically distinctive granulosa cell tumor that occurs 72% of the time before age 20 and almost 50% before 10.[73] Seventy percent of the tumors occurring before puberty are associated with isosexual precocious puberty. Bilaterality occurs in 3%, and many tumors are palpable preoperatively.[73,82]

The clinical behavior of this tumor appears less aggressive than adult granulosa cell tumors, although approximately 5% are clinically malignant and either present with or develop metastasis within several years. Conservative surgery such as unilateral salpingo-oophorectomy appears an effective treatment for most patients. Due to the indolent nature

of granulosa cell tumors and the infrequent occurrence of this tumor, considerably more follow-up is necessary before more definitive statements can be made about its biologic behavior.[73,82,86]

Thecoma-Fibroma Tumors

The tumors classified in this category almost always are benign. On rare occasions a fibrosarcoma or malignant thecoma may occur. The tumors occur with relatively high frequency in women with basal cell–nevus syndrome. Fibromas that are 10 cm in diameter may be associated with ascites and hydrothorax, the so-called Meig's syndrome. In Meig's syndrome, the effusions resolve after the involved gonad is removed and are not indicative of malignancy.[73]

Sertoli-Leydig Cell Tumors (Arrhenoblastoma)

Sertoli-Leydig cell tumors are quite uncommon (0.2% of all ovarian neoplasms), with a peak incidence at age 25. One-fourth of these tumors are in women under 20. It is possible that a familial pattern exists in women who also have thyroid disease. Three percent of these tumors are bilateral and in almost all reported series were confined to the ovary at initial diagnosis.[73,87]

Clinically, the tumor usually is androgenic but may be estrogenic or hormonally inert.[73,88] In postpubertal patients, the initial manifestation of an androgenic tumor is defeminization; actual masculinization is a late development.[87] The more poorly differentiated tumors may be more common in the younger patients and more likely to cause hormonal alterations. Some attribute a more malignant clinical course to the poorly differentiated tumor. Heterologous tissue is present in approximately 20% of tumors and also may indicate a more malignant nature.[73,87,88]

Patients desiring future childbearing usually are treated with unilateral salpingo-oophorectomy for stage I disease, and more aggressive surgical treatment is reserved for more advanced stage tumors or older women. Recurrence rates vary from 12 to 22%, and the mortality rate ranges from 3 to 33%. Most recurrences are recognized within 5 years of initial therapy, in contrast to the more common granulosa cell tumor that is notorious for late recurrences. The optimal management for patients with metastatic or recurrent disease is unknown. Several combination chemotherapy regimens appear active. The role of radiation therapy also is unknown.[73,83,87,88,88a]

Gynandroblastoma

This is an extremely rare tumor, diagnosed only when a single tumor contains unequivocal foci of both granulosa cell and Sertoli-Leydig cell elements. These tumors may be hormonally inert, androgenic, or estrogenic and appear to be low grade malignant tumors.[73]

Sex Cord Tumors with Annular Tubules

This tumor appears unique among the SCST because of its pathologic characteristics and frequent association with the Peutz-Jeghers syndrome (PJS). (In this regard, PJS also is associated with increased frequency of adenoma malignum of the cervix, a well-differentiated mucin-producing adenocarcinoma of the endocervix.[89]) The sex cord tumor with annular tubules (SCTAT) occurs in almost all female patients with PJS. The tumors are small (usually less than 3 cm), but 66% are bilateral. These tumors frequently are multifocal and discovered only incidentally after the ovaries are removed for unrelated conditions. When associated with PJS, SCTAT appears almost benign. In 47 patients with SCTAT without PJS, the tumors were usually large, unilateral, and associated with hyperestrinism. Twenty percent were metastatic, and 10% proved fatal.[73,89–91]

Epithelial Carcinoma

In childhood epithelial ovarian cancers represent only 12% of all malignant ovarian tumors, which is in sharp contrast to ovarian cancers found in other age groups where approximately 75% are epithelial.[3,11,15,16] Epithelial tumors show a wide range of biologic behavior dependent upon histologic grade, stage, and postoperative residual tumor. In general, younger patients usually have better-differen-

tiated tumors and earlier stage cancers, and therefore better 5-year survival rates.[24,92]

In 1971, the International Federation of Gynecologists and Obstetricians recognized a group of epithelial tumors that were histologically distinct and biologically less malignant than other invasive epithelial ovarian cancers. These tumors were labeled cystadenomas of low malignant potential, or borderline cancers. Histologically, borderline tumors have extensive papillary growth patterns with secondary and tertiary branching and stratification of the epithelium with cytologic atypia. The distinctive feature, however, is the lack of identifiable stromal invasion.[13,93,94] In some cases, the distinction between borderline and well-differentiated cancer may be quite difficult, and multiple sections of an ovarian tumor should be reviewed.[94] Importantly, the diagnosis of a borderline tumor is based upon the histologic appearance and not the clinical presentation. Approximately 70% of borderline tumors are stage I, 20% stage II, and 10% stage III. The 5-year survival rates for borderline epithelial tumors have been reported as 95% for stage I, 72% for stage II, and 50% for stage III. Consequently, advanced stage borderline tumors are biologically malignant, although less than the frankly invasive epithelial malignancies for which survivals are 63% stage I, 38% stage II, and 7% stage III.[13,93,95]

The extent of the tumor at the time of diagnosis and the amount of postoperative residual cancer are critical factors that influence survival in epithelial ovarian malignancies.[13,21,22] Surgical staging must be thorough and include histologic and/or cytologic evaluation of all visceral and parietal peritoneal surfaces, omentum, and retroperitoneal nodes.[13,21,22] For the young nulliparous patient with apparent stage IA epithelial ovarian cancer, conservation of the contralateral ovary and uterus may be done but can carry some risk because epithelial cancers are more frequently bilateral than other types of ovarian malignancies.[13,19,93] Since occult malignancy in an otherwise normal-appearing ovary has been reported in from 12 to 24% of cases, the contralateral ovary must be biopsied before preservation.[18,19,93,96] Other guidelines for conservative management in young, nulliparous patients are an otherwise normal pelvis, a desire to have children, a borderline or well-differentiated histology, a tumor that is encapsulated, unruptured, and free of adhesions and external excrescence, and a cytologic evaluation of the abdomen and pelvis that is negative of malignant contamination.[22]

Conservative surgery should not be considered until a complete surgical staging has been done. It has been recommended that the residual ovary be excised when childbearing is over.[18] When these guidelines have been followed, preservation of the contralateral ovary and uterus has not adversely affected 5-year survival rates.

The clinical significance of rupturing during removal of an otherwise stage I malignant epithelial ovarian tumor is unknown. Although earlier reports did not indicate that rupture was detrimental to 5-year survival, a recent report from the Mayo Clinic suggests that it might be.[19,24,97] Since malignant cells can potentially implant and germinate, it is plausible that rupture is detrimental. At present, however, there are no strict clinical treatment guidelines after the rupture of such a tumor. Some authorities prefer the intraperitoneal instillation of radioactive chromic-phosphate suspension, whereas others suggest a 6- or 12-month course of single agent chemotherapy followed by a laparotomy to make sure there is no persistent viable cancer.[13,18,22,97]

Once extraovarian malignancy is identified, surgery should consist of the extirpation of all recognizable disease if possible or a sufficient resection to reduce residual deposit to a maximum size of less than 1–2 cm in diameter. Such tumor reduction is substantiated by improved response rates to chemotherapy in the adequately resected group. Postoperatively, the preferred treatment consists of a cisplatinum–containing combination chemotherapy regimen or whole abdominal radiation as performed at the Princess Margaret Hospital.[21,23,24,98] Whole pelvis radiation therapy as the sole postoperative treatment usually is unsatisfactory because ovarian cancer affects the entire peritoneal cavity.

The 5-year survival rate for adults with stage III epithelial ovarian cancer was 5–9% in an October 1983 report by the American College of Obstetrics and Gynecology.[22] This survival rate should be improving, however, since the

full impact of aggressive surgical resection and cis-platinum–containing multiagent regimens has not yet been realized. In several recent studies, complete response rates have ranged from 37 to 47%. Also, the 2- and 3-year absolute survival rates appear improved after multiagent chemotherapy, and the time to relapse is markedly prolonged compared with either historical controls or patients randomized to single agent regimens.[99–102]

Second-look laparotomy or laparoscopy is considered most important in evaluating patients who have a complete response to chemotherapy. In most series, 50–65% of apparent complete responders will have identifiable disease upon surgical reevaluation of the peritoneal cavity.[99–102] The second-look operation could begin with laparoscopy, but should that fail to identify residual disease, a formal abdominal operation that includes retroperitoneal node sampling is imperative.[103] Patients in whom the second-look operation is negative may discontinue chemotherapy, although close observation is mandatory.[24,99,101,102] Approximately 90% of these patients will remain in clinical remission. Patients with persistent disease require additional postoperative treatment with either chemotherapy, radiation, or a combination.

Tumor markers so far have been unsuccessful in monitoring epithelial ovarian cancer. The search continues for an epithelial ovarian cancer antigen that will allow for the early detection of a malignancy or the chance to monitor patients who are apparently in clinical remission. Unfortunately, at present the ideal tumor marker has not been identified, and responding patients who have no clinical evidence of cancer following chemotherapy require operative exploration to determine if persistent subclinical disease is present.[104–106]

Ovarian Lymphomas and Leukemias

Patients with leukemia or lymphoma frequently have metastatic involvement of the ovaries revealed during autopsy.[107] However, it is rare for these diseases to present as ovarian tumors.[107–109] When an apparent primary ovarian lymphoma does occur, it is initially often misdiagnosed as a dysgerminoma or stromal tumor because it is rare and frequently lacks B-type symptoms or associated adenopathy.[107,108] It also is highly probable that often apparent primary ovarian lymphomas actually represent metastatic involvement of the ovaries from inapparent systemic disease. This argument is strengthened by the relative frequency (55%) of ovarian bilateral involvement.[5] Nevertheless, primary ovarian lymphomas probably do occur, since an occasional long-term survivor has been reported following surgical excision of the ovary with or without postoperative pelvic radiation therapy. One recent survey of primary ovarian lymphomas concludes that an entity of primary ovarian lymphoma is likely because the histologic appearance of the lymphoma in children's ovaries is so dissimilar to that usually seen in lymph nodes.[107] For example, 38% of the ovarian lymphomas in children under the age of 20 consist of a diffuse, small cleaved-cell lymphoma (Burkitt's and non-Burkitt's type), which contrasts sharply with the 9% incidence of similar histology in lymph nodes in this same age group. Also, primary ovarian Hodgkin's and lymphoblastic lymphomas were rarely, if ever, seen.[107]

According to several authorities, if primary ovarian lymphoma is bilateral, a bilateral salpingo-oophorectomy and hysterectomy should be done in combination with either postoperative chemotherapy or radiation.[5,107,108] In the patient with unilateral disease, conservation of the contralateral ovary and uterus is recommended, although postoperative chemotherapy still is advised.

Soft Tissue Sarcomas Arising from the Genital Tract

Approximately 6% of all malignant neoplasms in children are soft tissue sarcomas (STS), and the genital tract is a fairly common site of origin.[2] The peak incidence is between ages 1 and 5, with 70% occurring in the first decade. Most female children with genital STS present with vaginal bleeding or a polypoid mass projecting from the vaginal orifice. Microscopically, there is loose edematous stroma and primitive rhabdomyoblasts. Cartilage or bone also may be present. The frequency of lymph node metastasis in genital STS is 19%

for both sexes, but appears much more often in boys.[2,110,111] Norris and Taylor have reported a vaginal polyp with stromal atypia that has been seen in children and mistaken for sarcoma botryoides. The nonmalignant nature of this polyp is validated by the long-term survivorship after local excision only.[112]

Initially, genital sarcomas were treated by local resection, but local and distant recurrences were frequent. The addition of local radiation therapy only moderately improved local control, but did not prolong survival.[2,113] Despite more radical surgical resection, including pelvic exenteration, the survival rates remained dismal.[113,114] The current experience as reported by several investigators, including those involved in the Intergroup Rhabdomyosarcoma Study (IRS), demonstrates improved survival when chemotherapy is coupled with surgical resection of the tumor, regardless of whether local radiation therapy also is used.[110,111,114-116] Vincristine, dactinomycin, and cyclophosphamide is the most commonly administered chemotherapy regimen. Due to improved survival with postoperative chemotherapy, it is now recommended that surgery be less radical, and although complete excision of the primary tumor is still the ultimate goal of the surgeon, considerable emphasis also is placed on preserving as much normal tissue as possible. Radiation therapy currently is reserved for patients with postoperative residual disease, locally or in the regional lymph nodes.[110-116] In some cases, chemotherapy has been given preoperatively for cytoreduction and then continued postoperatively as maintenance therapy.[117] Although the optimal treatment regimen has not been developed, there has been marked improvement in survivorship; 3-year relapse-free survival recently has been reported between 82 and 84% for patients with completely resected localized disease, 62 and 70% for patients with microscopic residual or regional nodal disease, 57% for patients with residual macroscopic disease, and even 29% for those who have distant metastases.[2]

Premalignant and Malignant Lesions of the Cervix, Vagina, and Vulva

Premalignant or dysplastic lesions of the lower reproductive organs are asymptomatic and often inconspicuous on examination. Histologically, there is disarray of the architectural structure of the epithelium and cytoplasmic and nuclear atypia. The etiology of the lesion is not known, although a viral agent is suspected.[118,119] Historically, these lesions have been seen most often in women over 35; however, the incidence is increasing dramatically in teenagers.[120-122]

The malignant potential of cervical intraepithelial neoplasia is unknown. Spontaneous regressions do occur, especially in grades I and II (mild or moderate dysplasia). Although the high grade intraepithelial lesions (severe dysplasia and carcinoma in situ) are more likely to progress than the lower grades, progression is seen in all grades and there is no predicting which lesion will progress or the time interval of progression.[120-122]

Most cervical and vaginal intraepithelial lesions are first recognized cytologically after a routine Pap smear. Colposcopy is the preferred method of evaluation for the recognized lesion unless it is a visible exophytic lesion or ulcer that can be biopsied without magnification. Because of the unpredictable false-negative rate in Pap smear evaluations, there is no justification for deferring colposcopy until another Pap smear has confirmed the abnormality.[120-123]

Colposcopy is the technique whereby the cervix is viewed with magnification and the epithelial and vascular pattern is examined to identify the origin of the abnormal cells. The most abnormal area can be precisely delineated and biopsied to allow the most accurate assessment of the cervix. If the entire area at risk (transformation zone) and the lesion have been seen and invasive cancer has been excluded, the intraepithelial lesion can be managed conservatively with either cryosurgery or laser surgery.[120-127] If invasive cancer cannot be excluded or if a lesion extends into the cervical canal and is beyond visualization, cervical conization must be done. Conization should be avoided as a routine evaluation in young women since the anatomic disruption of the cervix has been associated with subsequent pregnancy complications.[128-130]

Cryosurgery and laser surgery have been used extensively to treat vaginal and cervical intraepithelial lesions Essentially 90% of patients are successfully treated with either me-

thod. Cryosurgery is less expensive and requires less training. Colposcopically directed laser surgery, however, allows for better visualization of the lesion during treatment. Laser treatment has been associated with less cervical scarring, allowing for more thorough posttherapy colposcopic examinations.[124,127]

For multifocal vaginal disease the topical application of 5-fluorouracil has been used successfully, and occasionally total excision of the vaginal epithelium with skin grafting has been required.[131-133]

Vulvar intraepithelial lesions may be treated by localized excision of the individual lesions with either traditional or laser surgery. Occasionally, a patient with diffuse multifocal disease will require superficial "skinning" vulvectomy with skin grafting.[134-137]

Invasive epithelial carcinoma of the cervix, vagina, and vulva is extremely uncommon in adolescence and childhood. Such lesions should be treated by traditional radiotherapy or radical surgery, depending on the individual case.[95]

Precancerous and Invasive Cancer of the Uterine Corpus

Although endometrial adenocarcinoma is the most frequent gynecologic malignancy, it rarely appears in women under 20. Isolated cases have been reported, however. The predisposing factor for this malignancy appears to include a hormonal milieu of unopposed estrogen stimulation. The estrogen may be either exogenous or endogenous. It is unknown whether the estrogen is a carcinogen or cocarcinogen.[138-143]

Young women with either endometrial hyperplasia, carcinoma in situ, or endometrial cancer have an unopposed estrogen stimulation of the uterus. Clinically this occurs in those with Turner's syndrome who are given exogenous estrogens or in women with polycystic ovarian disease (PCO).[138-142] Women with PCO have estrogen excess resulting from extraglandular aromatization of biologically inactive androgens that are converted to estrone. Due to the hormonal milieu, ovulation is very infrequent, so the progesterone production needed to counteract the estrogen influence is limited.[139-141]

When a young woman has an endometrial hyperplasia or carcinoma in situ diagnosed by endometrial curettage, the preinvasive lesion can be treated with progesterone antagonism.[95,138] The more severe lesions must be monitored closely with periodic assessment of the endometrium, using curettage if necessary. Hysterectomy may prove necessary in patients who are unresponsive to progestin therapy.

When an adenocarcinoma occurs in the endometrium, hysterectomy, bilateral salpingo-oophorectomy, and intraoperative staging are necessary. A decision for postoperative radiation therapy in most cases can be based upon examination of the surgical specimen.[95]

Gestational Trophoblastic Neoplasia

Gestational trophoblastic neoplasms (GTN) include hydatidiform mole, invasive mole, and choriocarcinoma. In the United States, the incidence is approximately one in 1200 pregnancies. The occurrence of hydatidiform mole is greatest in those under 20 and over 40. Approximately 15% of patients with hydatidiform mole will have a malignant sequela. Thus, all patients need to be monitored closely. Choriocarcinoma is very uncommon and occurs at the rate of one in 20,000 to 40,000 pregnancies.[144,145]

The classic complete hydatidiform mole occurs without an embryo and usually has a 46,XX karyotype that is homozygous for one set of paternal genes. Even the occasional 46,XY complete mole results from two separate sperm fertilizing an "empty" egg. Both moles are linked to a propensity for choriocarcinoma.[146-148] In contrast, the partial mole is accompanied by a fetus and has a triploid 69,XXY karyotype. Malignant sequelae are very uncommon following a partial molar pregnancy.[149] Both complete and partial molar pregnancies seem to occur with equal frequency in women under 20 and represent about 35% of all diagnosed hydatidiform moles. Despite the relatively more benign course associated with a partial mole, all patients need to be followed both clinically and with sequential β-subunit HCG levels after evacuation of the uterus.[144-149]

Hydatidiform mole usually presents with uterine bleeding, an inappropriately sized uterus for the pregnancy duration, and hyperemesis. Toxemia may occur during the first 20 weeks of gestation. Anemia, infection, hyperthyroidism, and coagulopathy also may occur. The disease is confirmed by the observation of small grapelike vesicles passing from the uterus, failure to identify an intrauterine fetus, or the classical snowflake pattern seen in ultrasonography. Theca-lutein cysts are seen in 15–20% of patients.[144,145]

Primary therapy includes uterine evacuation by suction curettage. Prostaglandins may be beneficial in the uterine evacuation of a partial mole with a coexistent fetus. Hysterectomy or hysterotomy are rarely indicated, especially in those under 20. After suction curettage, a gentle sharp curettage of the endometrium may allow for the identification of the invasive mole. Occasionally a patient, as a result of the intravenous embolization of trophoblastic tissue, will have acute respiratory insufficiency following an evacuation. Theca-lutein cysts do not require surgical removal.[144,145]

Adequate contraception must be encouraged following an evacuation. Oral contraceptives do not appear to increase the risk of malignant sequelae and are the preferred method of birth control.[145,149] In addition to 6 to 12 months of adequate contraception, serial radioimmunoassays for β-HCG must be done weekly until normal levels are achieved, then every 2 weeks for 2 months, and finally, monthly for 6 to 12 months. Close monitoring of HCG will allow early detection of patients with atypical regression curves or plateaued or rising titers. Such patients require evaluation for malignant GTN.[144,145,150,151]

Malignant GTN usually follows hydatidiform mole but can occur after ectopic pregnancy, spontaneous and therapeutic abortion, or term pregnancy. Once malignant GTN has occurred treatment is based upon the clinical staging, rather than histology. This staging includes biochemical and radiographic studies for pulmonary, renal, liver, and brain metastases. The staging for malignant GTN is most important since it influences the intensity of the subsequent treatment.[144,152–156] Patients with no identifiable metastasis (nonmetastatic category) can be treated with either single agent methotrexate or actinomycin D chemotherapy. During chemotherapy β-HCG levels are monitored weekly, and chemotherapy continues as long as the disease appears to be regressing. After three consecutive negative weekly titers chemotherapy may be discontinued, but HCG monitoring must continue. Tumor progression during treatment, as evidenced by the development of metastasis or rising HCG titers, is a poor prognostic indicator and demands a more aggressive multiagent chemotherapy. In most centers, 100% of patients with nonmetastatic disease survive.[144,152,156]

Patients with metastatic GTN are divided into a "good" or "poor" prognostic category that is based upon the staging evaluation. Good prognostic patients may be treated in a similar fashion to those with nonmetastatic disease. In most centers, almost 100% of the patients in this category survive.

Patients enter a poor prognostic category when staging reveals the following:

1. Initial urinary HCG titer is in excess of 100,000 IU/24 hour urine collection or serum HCG titer is greater than 40,000 mIU/ml.
2. The duration of symptoms has exceeded 4 months.
3. Brain or liver metastasis is found.
4. Progressive metastases had developed during previous treatment with chemotherapy.
5. Malignant sequelae occur after full-term pregnancy.

Patients in this category require aggressive multiagent chemotherapy, possible concomitant radiation to the brain and liver, and considerable expertise in management. The survival rate for this category is approximately 65%.[144,152–156]

Impact of Chemotherapy on Menstrual and Reproductive Function

Oligomenorrhea and amenorrhea frequently develop during or after single or multiagent cytotoxic chemotherapy. The alteration in menstrual function is believed due to a chemotherapy-induced ovarian failure documented by low estradiol and high gonadotropin serum levels and a histologically identi-

fied reduction in primordial follicles and ova as seen on ovarian biopsy.[157-162] Women over 30 tend to have menstrual alterations earlier in the treatment and are more likely than younger women to have permanent amenorrhea and sterility after completing chemotherapy. The effect of age appears more significant than the total dosage of specific drugs.[157] The addition of radiation therapy—even with ovarian shielding (such as might be used for total nodal lymphoid irradiation)—results in the most marked and persistent alterations in menstrual function.[157] Many women who have normal menses during therapy may notice a gradual decrease in menstruation and premature menopause after completing their treatment. Although it has been suggested that hormonal suppression of follicular development during chemotherapy may prevent premature ovarian failure, taking combination oral contraceptives during chemotherapy does not appear to confer a lasting benefit on ovarian function.[157,160] Even women who have a return of normal menses following intensive chemotherapy appear to be at increased risk of premature ovarian failure. Considering the metabolic consequences of long-term estrogen deficiency, treatment planning should include an option for the preservation of ovarian function in patients who require pelvic irradiation.[163-165]

Fertility is a frequent consideration for the young patient who survives her malignancy. Recently, several reports have addressed the impact of intensive cancer therapy on subsequent fertility.[163-169] Normal pregnancies have occurred after the successful treatment of germ cell neoplasms of the ovary, supporting the opinion presented in this chapter that conservative surgery should be considered in the appropriate patient.[165-167] The subsequent pregnancies in women who were previously treated with chemotherapy for gestational trophoblastic disease do not show an increase in congenital anomalies, although there may have been an increase in spontaneous abortion.[163,164] Normal live births also have been reported in one series of women treated with multiagent therapy and sometimes total lymphoid radiation for Hodgkin's disease.[168] In contrast, however, other reports suggest that chemotherapy or combination chemotherapy-radiation protocols are associated with an increased risk of congenital malformation.[170,171] Such contradictions underscore our lack of basic knowledge on this issue, so we must advise our patients that we do not know the full impact of intensive anticancer therapy on developing ova or subsequent generations. In addition to counseling patients on the theoretical risks involved, in the event of conception we should offer early fetal evaluation with ultrasonography and/or genetic amniocentesis.

Psychologic Support

It has been the attempt of this chapter to provide a comprehensive survey of gynecologic cancers in children, and the author has concentrated on the current medical and scientific information available. Before concluding it is important to consider the psychologic impact that is so crucial in the care of young patients.

Cancer is a traumatic diagnosis at any age but may be particularly so for the child or adolescent because of fear of the unknown, fear of physical separation from family during hospitalization, isolation from peer groups, and uncertainty about the future. The adolescent may be particularly sensitive to the physical changes of radical surgery or chemotherapy, the constraints of a rigid schedule of therapist and appointments, and the possible loss of femininity and future motherhood. To overcome these fears and frustrations a child needs support from parents, family, and friends, as well as from counselors, social workers, psychologists, and the oncologist. Together this team should be able to inform the child of her illness in terms that are understandable, and in turn, the child should be encouraged to share her concerns with members of the team. When such an atmosphere of cooperative understanding and trust has been established, the child with malignant disease can be adequately cared for and her parents appropriately supported.

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Diethylstilbestrol Exposure in Utero 12

Elizabeth K. Senekjian and Arthur L. Herbst

The nonsteroidal estrogen diethylstilbestrol (DES) was synthesized in 1938 by Dodds and associates.[1] The use of DES for the prevention and treatment of abortion and late pregnancy complications such as toxemia, premature and postmature delivery, stillbirth, and neonatal death[2,3] was suggested by Smith in 1946,[4] and its use became widespread. In 1953 two prospective controlled studies refuting the drug's previously ascribed advantages were published by Ferguson[5] and Dieckmann.[6] The use of DES for pregnancy support has since appeared to have diminished.

In 1970 Herbst and Scully observed an unprecedented number of cases of adenocarcinoma of the vagina in young women ranging in age from 15 to 22.[7] The association of antenatal DES exposure with the subsequent development of vaginal clear cell adenocarcinoma was identified by a retrospective epidemiologic investigation using matched control cases.[8] These reports and the evidence from Greenwald[9] induced the Food and Drug Administration in 1971 to ban the use of DES during pregnancy.[10] It is estimated that between the late 1940s and 1971 2–3 million pregnant women received DES, resulting in the in utero exposure of up to 1.5 million female offspring.[11]

Clear Cell Adenocarcinoma

Demography

In 1971 the Registry of Clear Cell Adenocarcinoma of the Genital Tract in Young Females (now called the Registry for Research on Hormonal Transplacental Carcinogenesis) was established to collate information on the epidemiology, history, and pathology of these malignancies for women born after 1940. All cases of vaginal and cervical clear cell adenocarcinoma regardless of whether the mother received pregnancy hormonal treatment are accessioned. Genital cancers in females exposed to any antenatal hormonal therapy are also included.

To date, the Registry has studied 497 cases of clear cell adenocarcinoma. Of the 466 subjects with accessible maternal histories, 63% had in utero exposure to DES or synthetic estrogen analogs. No evidence of maternal hormone ingestion was found in 25%. Nine percent were treated for high risk pregnancy, but the medication taken could not be definitely identified. In addition, there were 12 cases in which the record indicates the use of progestin with or without steroidal estrogen.[12]

The risk of clear cell adenocarcinoma in a DES-exposed female under 24 is 0.14 to 1.4 per 1000. Since the precise number of women treated with DES during pregnancy cannot be determined, this calculation is based upon estimates (from drug marketing data) of the number of liveborn females exposed to DES and Registry data of the incidence of DES-associated clear cell adenocarcinoma for 1951 to 1953.[13] It was during these years that the use of DES during pregnancy peaked and that the largest number of DES-exposed women who have developed adenocarcinoma were born.

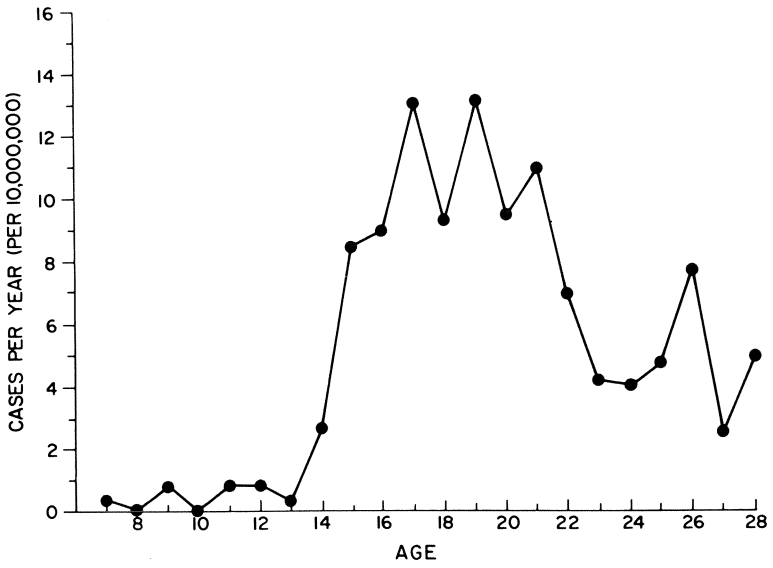

Figure 12-1. Incidence of clear cell adenocarcinoma by age at diagnosis among white females born in the United States. Reproduced with permission from Herbst AL, Bern HA (eds): Developmental Effects of Diethylstilbestrol (DES) in Pregnancy. New York, Thieme-Stratton, 1981.

DES-related clear cell adenocarcinoma has been diagnosed in females between ages 7 and 33, with 95% occurring in those 14 and older. The age incidence curve rises at 14 and extends as an irregular plateau between 17 and 21 (Fig. 12-1). The median age at detection is 19,[14] suggesting that the hormonal alterations at menarche may play a role in the evolution of adenocarcinoma, a hypothesis that is unproven. The incidence of these malignancies among DES progeny older than 30 cannot be determined as yet.

Clinical Features and Therapy

Fifty-seven percent of Registry cases originated in the vagina, while the remainder were in the cervix.[15] Cervical tumors have in most cases involved the ectocervix (Fig. 12-2) and have rarely been limited to the endocervix. Vaginal carcinomas usually are located in the upper one-third of the vagina, along the anterior wall (Fig. 12-3); they are seldom located in the lower one-third. The tumors have varied from 1.0 mm to more than 10.0 cm in diameter; the majority have had an exophytic or nodular configuration with necrosis and hemorrhage, whereas others have formed flat lesions, occasionally with ulceration. A few rare tumors are confined to the lamina propria. Because they are concealed by squamous epithelium they cannot be seen and elude colposcopic detection. Diagnosis is made by careful palpation and biopsy.

Figure 12-2. Clear cell adenocarcinoma of the cervix; hood over anterior cervix. Reproduced with permission from American College of Obstetricians and Gynecologists: Intrauterine Exposure to Diethylstilbestrol in the Human. Washington, DC, ACOG, 1978.

The classification of the International Federation of Obstetrics and Gynecology (FIGO) is used for staging vaginal and cervical adenocarcinoma (Table 12-1). Dissemination

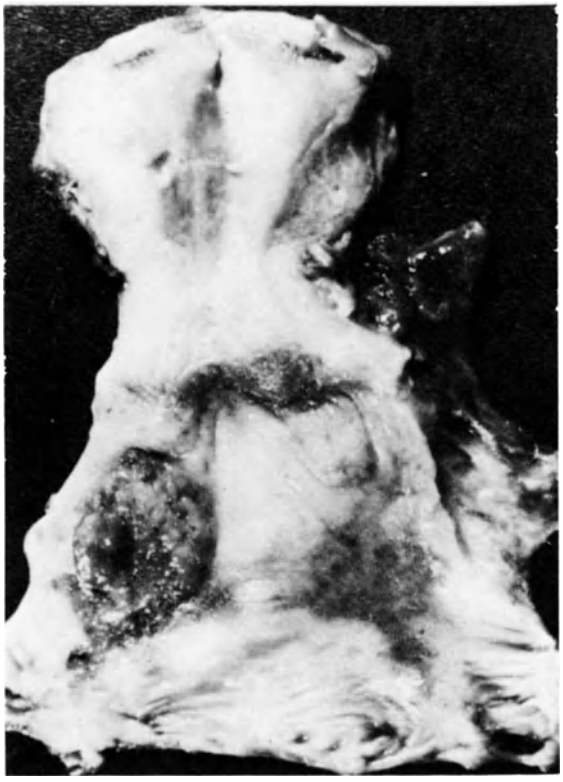

Figure 12-3. Clear cell adenocarcinoma of the vagina, anterior wall. Reproduced with permission from Cancer 25:745, 1970.

Table 12-1. FIGO Classification of Vaginal and Cervical Carcinoma.

	Carcinoma of the Vagina
Stage I	Confined to the vaginal wall
Stage II	Invades the subvaginal tissue; no extension to the pelvic wall
Stage III	Extends to the pelvic wall
Stage IV	Involves the mucosa of the bladder or rectum or extends beyond the true pelvis
Tumors involving the external cervical os are classified as cervical carcinomas; tumors involving the vulva are classified as vulvar carcinomas.	
	Carcinoma of the Cervix
Stage I	Confined to the cervix
Stage IIA	Involves the upper two-thirds of the vagina; no obvious parametrial infiltration
Stage IIB	Parametrial infiltration; no extension to the pelvic wall
Stage IIIA	Involves lower third of the vagina; no extension to the pelvic wall
Stage IIIB	Extends to the pelvic wall and/or includes hydronephrosis or nonfunctioning kidney
Stage IV	Involves mucosa of the bladder or rectum or extends beyond the true pelvis.

usually occurs by local spread and metastases via lymphatics and/or vascular channels. Tumor extent, volume, and depth of invasion correlate with the frequency of lymph node involvement.

The prevailing therapy for stage I adenocarcinomas and early stage II vaginal and stage IIA cervical lesions has been radical hysterectomy, partial or total vaginectomy, pelvic lymphadenectomy, the creation of a neovagina via split thickness skin graft, and ovarian preservation. Larger lesions and more advanced carcinomas have been treated with conventional radiation of the primary tumor and regional lymphatics. Selected large lesions invading the bladder anteriorly or the rectum posteriorly have been treated by pelvic exenteration.

Some modifications of the treatment have been introduced in an attempt to conserve fertility, but such efforts should not compromise therapeutic effectiveness. Twenty-seven Registry patients underwent local excision or total or partial vaginectomy for small adeno-

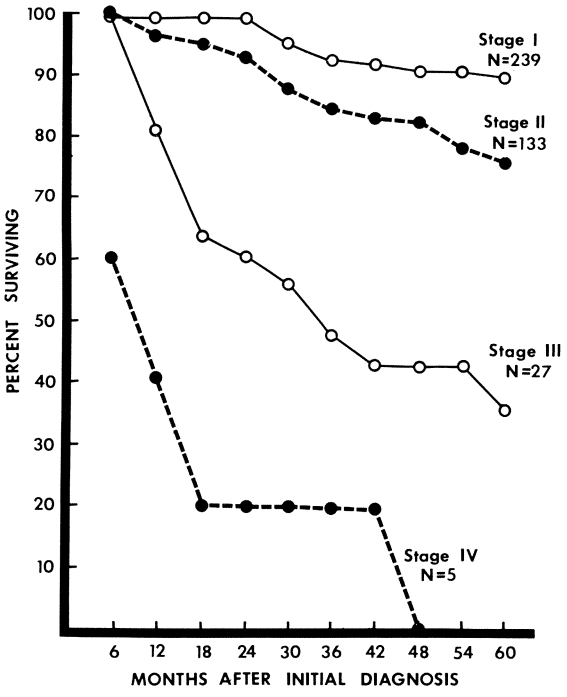

Figure 12-4. Survival of patients according to stage of clear cell cervical and vaginal adenocarcinoma. Reproduced with permission from Nichols DH, Evrard J (eds): Diagnostic and Ambulatory Gynecology. Philadelphia, Lippincott, 1984.

carcinomas; five have since become pregnant. Nevertheless, six recurrences and two cancer-related deaths in those who have had local vaginal excision as their sole treatment have discouraged this approach.[12] A feasible therapeutic alternative that avoids compromise of reproductive potential yet rules out lymph node spread has been retroperitoneal lymphadenectomy with excisional biopsy of the primary tumor. This is followed by limited irradiation via transvaginal cone and/or interstitial radiation therapy to the primary tumor bed. To avoid cervical stenosis, it is preferable that the vaginal tumor not be adjacent to the cervix.[16,17]

Prognosis has varied with stage, lymph node metastasis, and histology. Five-year actuarial survival of Registry cases with stage I vaginal and cervical adenocarcinoma has been 90%, stage II vaginal and stage IIA cervical tumors 82%, stage IIB cervical lesions 60%, and stage III cancers 37% (Fig. 12-4). Five-year survival has been 80%[16] for all patients with clear cell adenocarcinoma.

Anatomic Abnormalities of the Reproductive Tract

Numerous nonmalignant abnormalities such as cervical ectropion, vaginal adenosis, and structural variations of the cervix, vagina, uterine corpus, and fallopian tubes have been found in DES-exposed females.

Anomalies of the Lower Müllerian Tract

Vaginal and Cervical Epithelial Changes

Cervical ectropion is glandular (columnar) epithelium or its mucinous products in the ectocervix. The term "adenosis" is used when these changes occur in the vagina (Fig. 12-5). In one study of biopsy materials, adenosis was confined to the upper half of the vagina in 87% of the DES females, with changes typically in continuity with ectropion. Adenosis in the lower half of the vagina was noted in only 9% of cases, while only 4% had total vaginal involvement.[18]

Columnar epithelium may involve the vaginal surface as well as glands within the lamina propria. Two cell types compose columnar epithelium of adenosis. The cells of the endocervical (mucinous) type resemble those

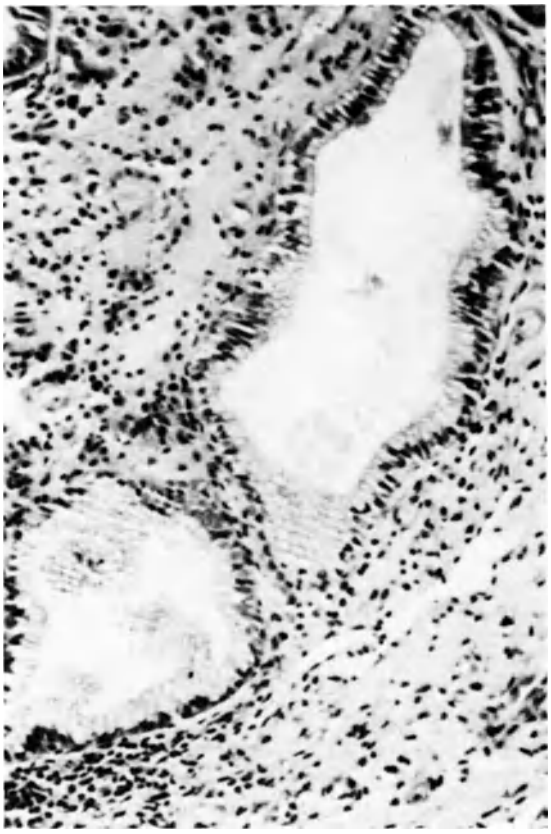

Figure 12-5. Vaginal adenosis; glands lined by mucinous cells × 200. Reproduced with permission from Cancer 25:745, 1970.

of the endocervix and are found in the majority of biopsy samples of adenosis. The tuboendometrial cells, which resemble the cells of proliferative endometrium or fallopian tube epithelium, are found more commonly in adenosis of the lower vagina than in samples from the upper vagina.

With the passage of time, ectropion and vaginal adenosis frequently undergo repair as columnar epithelium is supplanted by squamous metaplasia which occasionally progresses to fully glycogenated squamous epithelium. Serial colposcopic, cytologic, and histologic evidence demonstrates progressive spontaneous regression of columnar epithelium with longer periods of observation and in older subjects.[18–20]

In 1975, Herbst et al demonstrated adenosis in 73% of cases where DES exposure was begun prior to the eighth week of pregnancy, but in only 7% when treatment was initiated at or

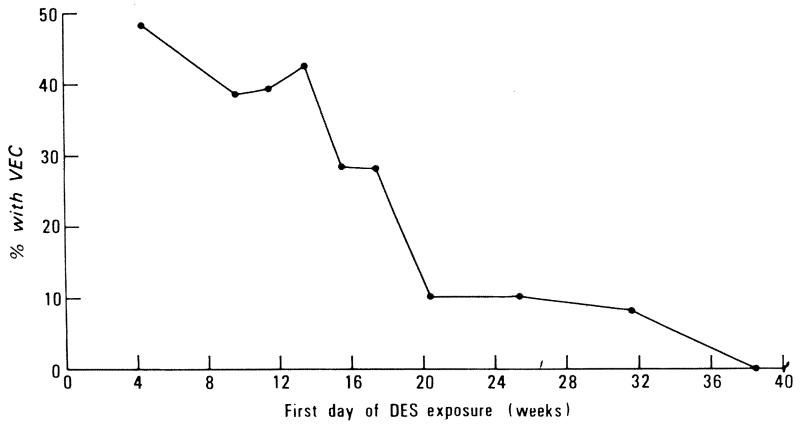

Figure 12-6. Frequency of VEC relative to first day of DES exposure in utero. Based upon record review of 1093 individuals. Reproduced with permission from Obstetrics & Gynecology 53:300, 1979.

following the 18th week.[21] The National Cooperative Diethylstilbestrol Adenosis (DESAD) Project was established in 1974 to study the effects of DES exposure. In 1979, the multicenter collaborative DESAD study published results of the colposcopic findings from 3212 women. The data related both the total DES dosage and the time the drug was initiated during pregnancy with the frequency of vaginal epithelial changes (VEC), which are defined as the colposcopic and histologic changes that correspond to adenosis and/or squamous metaplasia. These changes were noted in only 8% of the cases where exposure was after the 18th week, but did occur occasionally even when treatment was begun after the 30th week. A higher incidence of VEC was associated with DES exposure prior to the 18th week of gestation (Fig. 12-6) and in cases where total dosage surpassed 2500 mg. The frequency of VEC after age 27 decreased, presumably as a result of progression to normal epithelium.[20]

Cervicovaginal Structural Abnormalities

Anatomic malformations of the cervix and vagina have been found in 18–58% of DES-exposed offspring.[22,23] Vaginal abnormalities include incomplete transverse septa, obliteration of the fornices, and ridges. Cervical changes consist of complete and incomplete collars, hoods, protuberances or cock's combs, pseudopolyps, hypoplasia, and stenosis of the endocervical os (Fig. 12-7).

The cervicovaginal hood (CVH) may regress in some women with time. Antonioli et al noted CVH at initial evaluation in 123 DES-exposed females. Under prolonged observation, CVH was found to decrease in 24% and completely resolve in 28%. It should be noted, however, that the CVH remained unchanged in almost half of those studied.[24]

Squamous Intraepithelial Neoplasia

An extended transformation zone is found in most DES-exposed subjects as a result of columnar epithelium over the cervix and extending into the vagina. Colposcopically abnormal areas showing white epithelium, punctuation, and mosaicism have been described in one study in as many as 97% of DES-exposed offspring.[25] However, directed biopsies from these colposcopically abnormal areas often have shown only metaplastic squamous epithelium. Welch et al identified squamous metaplasia in four-fifths of colposcopically directed biopsy specimens, while hyperkeratosis was seen in 20%, and mild dysplasia was diagnosed in only one of the 215 samples.[26]

In a study by Burke et al, a diagnosis of dysplasia on biopsy was more likely when colposcopically detected white epithelium and mosaicism were located in the cervix rather than in the vagina. Ten of 53 women with cervical white epithelium compared to only two of 182 with vaginal white epithelium had histologic evidence of dysplasia. In addition,

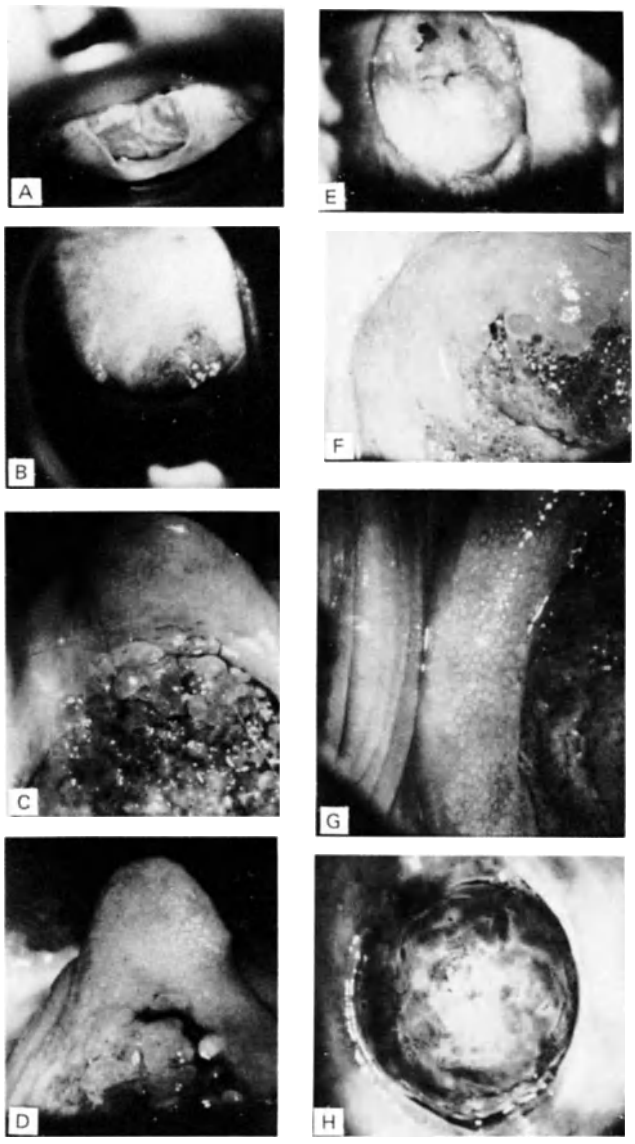

Figure 12-7. Cervicovaginal structural abnormalities. **A** Incomplete circumferential vaginal septum. **B** Incomplete vaginal septum. **C** and **D** Cock's comb defect of uterine cervix. **E–G** Complete cervical collars. **H** Endocervical stromal hyperplasia (pseudopolyp). Reproduced with permission from Herbst AL, Bern HA (eds): Developmental Effects of Diethylstilbestrol (DES) in Pregnancy. New York, Thieme-Stratton, 1981.

five of 39 women with cervical mosaic lesions compared to none of 96 with vaginal mosaicism demonstrated dysplasia on biopsy.[19]

An enlarged transformation zone in the DES-exposed cervix has led to concern that intraepithelial squamous cell neoplasia may occur with increasing frequency. However, recent results from case control studies have not confirmed an increase. The DESAD collaborative study reported dysplasia at initial evaluation in only 2.1% of 1400 females who had no prior history of squamous cell abnormality; three had moderate dysplasia, while the remainder had mild dysplasia. Severe dysplasia and carcinoma in situ were only detected in those referred with the diagnosis of intraepithelial neoplasia, nine of 24 cases.[27] A subsequent study of 4589 women revealed dysplasia of the cervix and vagina in 1.8% of DES-exposed females who were identified by prenatal records; a somewhat higher percentage of dysplasia was found in referral patients.[28]

The reported incidence of intraepithelial

neoplasia in the DES-exposed female has fluctuated between 0 and 18%.[19,27] Factors contributing to this variabiilty include the method of patient selection, age, number of sexual partners, and especially the misdiagnosis of dysplasia in those with immature squamous metaplasia.

Newer techniques have been introduced to aid in the correct identification of immature squamous metaplasia that is so common in the DES-exposed. The estimate of nuclear DNA content with Feulgen spectrophotometry has been of value.[29] Squamous metaplasia demonstrates the euploid pattern, the normal diploid distribution (2N). Atypical metaplasia and minimal dysplasia are usually polyploid, containing multiples of the diploid distribution (4N, 8N). Sporadically, minimal dysplasia, frequently, moderate dysplasia, and invariably, severe dysplasia exhibit aneuploidy, which is characterized by a wide range of DNA values and reflects major chromosomal abnormalities. The technique is laborious and primarily a research tool. It is important not to start therapy in the DES-exposed unless a reliable diagnosis of dysplasia has been established.

Anomalies of the Upper Müllerian Tract

Uterine Structural Malformations

Abnormalities of the shape of the uterus as identified by hysterosalpingogram were described by Kaufman in 1977.[30] These included a T-shaped uterine cavity, hypoplasia of the uterine cavity, constricting bands within the cavity, enlargement of the lower uterine segment, synechiae, irregularity in the wall of the endometrial cavity, and distension of the proximal portions of the fallopian tubes (Fig. 12-8). Females with cervicovaginal anatomic changes or VEC were more likely than those without changes to have an abnormal hysterosalpingogram.[31] Haney, using linear planimetry, quantified these radiographic changes and showed a significant decrease in the size of the endocervical canal, upper segment, and endometrial cavity surface area in DES-exposed women compared to control subjects.[32]

Further analysis of the data indicated a significantly larger proportion of DES-exposed progeny had such radiographic abnormalities when DES therapy was begun at or prior to the 12th week of gestation, as opposed to initial exposure after the 18th week. Total dosage of DES and age at examination did not correlate with upper tract changes.[31]

Fallopian Tube Defects

DeCherney et al have reported structural changes of the fallopian tube.[33] These include a foreshortened, convoluted oviduct with "withered" fimbria and a pinpoint os. The alterations were observed in 16 DES-exposed women at the time of laparoscopy, but none were evident by hysterosalpingography.[33]

Evaluation and Management of DES-Exposed Females

Methods of Examination

The evaluation of DES-exposed progeny or anyone suspected of having in utero exposure should begin after the onset of menses or by age 14. Because the use of DES during pregnancy was prohibited in 1971, most DES daughters have by now reached menarche. The peak years of DES use were 1946 through 1953; thus the majority of exposed women currently are between 29 and 39. Antenatal DES exposure alone is not sufficient justification for examining the premenarchal female. However, abnormal bleeding or discharge does require evaluation at any age.

Examination of the very young or premenarchal patient may be done under light anesthesia with a small caliber speculum or a lighted urethroscope. A cotton-tipped, saline-moistened applicator can be used to obtain a cytologic specimen. The vagina and rectum should be digitally examined. Because the vaginal epithelium may not stain with iodine due to the lack of estrogen stimulation prior to menarche, the application of Lugol's solution (see below) should be omitted.

Inspection and Palpation

Examination of the postmenarchal female includes external inspection followed by careful digital palpation of the entire vagina and cervix; lower genital structural changes and nodularity may be detected. This approach

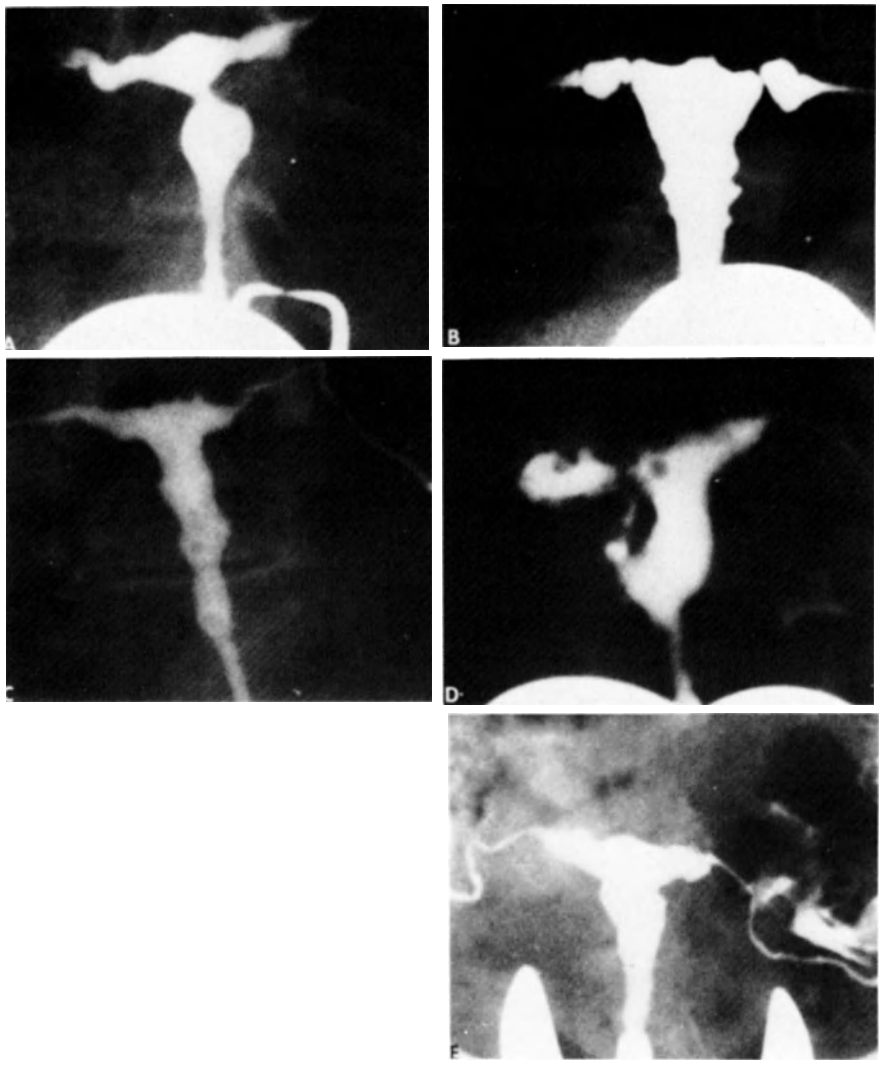

Figure 12-8. Uterine anomalies. **A** T-shaped uterus with constriction. **B** Hornlike extensions from proximal constriction; irregular uterine cavity. **C** T-shaped uterus; narrow, irregular cavity. **D** Multiple intrauterine defects; irregular cavity. **E** T-shaped uterus; irregular borders.

Reproduced with permission from American Journal of Obstetrics & Gynecology 137:299, 1980; and Herbst AL, Bern HA (eds): Developmental Effects of Diethylstilbestrol (DES) in Pregnancy. New York, Thieme-Stratton, 1981.

may reveal a malignancy situated beneath an intact mucosa. A speculum of suitable size is introduced, rotated, and slowly withdrawn. Cytologic samples should be obtained routinely and separately from the endocervix, ectocervix, and throughout the vagina. The use of lubricating jelly will impair accurate cytologic interpretation, thus only water should be used.

The anxious, young teenager may require a second examination 3 to 6 months after the initial visit. Tampon use during menses may facilitate subsequent exams. A Pedersen speculum with longer and narrower blades is helpful when examining a virgin.

Colposcopy

Colposcopy is done to define the limits of the transformation zone and to locate the most abnormal patterns; it is essential in the evaluation of an abnormal cytologic smear. The colposcopic appearance of adenosis is similar to the grapelike columnar epithelium seen in nonexposed females. The surrounding transformation zone may contain areas of punctu-

ation and mosaicism which usually represent metaplastic squamous epithelilum rather than dysplasia. Surface contour and distance between vessels can be helpful in differentiating between intraepithelial neoplasia and squamous metaplasia.

Iodine Staining

Painting the cervix and the entire vagina with half-strength Lugol's solution is recommended for each examination. Glycogen-poor tissue, which includes adenosis, immature metaplasia, and dysplasia, will not stain with iodine. Therefore, the margins of the cervical transformation zone or the extent of VEC can be outlined, and the natural history of the subsequent changes can be accurately followed.

The benefit of thorough evaluation of the DES-exposed patient has been emphasized by the rare appearance of clear cell adenocarcinoma in nine patients being followed for vaginal adenosis. Palpation has elucidated neoplasms as small as 3.0 to 5.0 mm. Preliminary identification of adenocarcinoma by cytology also has been reported.[34] Colposcopy has not been of significant value in the early detection of clear cell adenocarcinoma in part because the tumors do not present with an altered vascular pattern.

Management and Follow-up

In the absence of biopsy evidence for intraepithelial neoplasia, treatment of nonstaining epithelium or areas of columnar and metaplastic epithelium is not indicated. Attempts to eradicate VEC with cryosurgery, cauterization, and excision have in some cases led to complications such as stenosis of the cervical os with the potential of increasing the risk of infertility. For example, cervical stenosis was noted in 74% of 42 patients who underwent cryocautery and also after electrocautery in one of four patients.[35] Intraepithelial neoplasia requires individualized management. Laser vaporization has been adapted for treating advanced lesions such as severe dysplasia or carcinoma in situ. Follow-up may be recommended for the less advanced lesions such as mild dysplasia, particularly in view of the problem of differentiating mild squamous atypia from immature squamous metaplasia.

An annual examination is usually performed in DES-exposed females who have both a normal cytologic examination and a transformation zone that is confined to the cervix. For those subjects with large transformation zones that extend into the vagina, semiannual evaluations are often done. If cellular atypia or intraepithelial neoplasia is diagnosed, more frequent follow-up may be advisable depending upon the degree of atypia, the severity of dysplasia, and the necessity of treatment.

Contraception

The best type of contraception for the DES patient has not been established. The DESAD Project reported that more than 60% of the 339 women studied used oral contraceptives without any apparent adverse effects on vaginal adenosis or cervical ectropion.[20] Although the cumulative lifetime estrogen dosage taken by the DES-exposed female has been of theoretical concern, there is no established contraindication to the use of oral contraceptives for this group.

The use of barrier contraceptives such as jellies, foams, creams, and the diaphragm frequently has been advocated because they have no systemic effects. The cervical and upper vaginal epithelium may become thicker with frequent use of the diaphragm. These areas of hyperkeratosis have no atypia and appear to regress after use is discontinued. No reports describe complications in DES-exposed women who have intrauterine devices. However, Herbst et al reported a higher frequency of pelvic inflammatory disease in the DES-exposed group,[36] which has led to some caution in prescribing the intrauterine device for women exposed to DES in utero.

Reproductive Function

Menstrual Pattern

There are conflicting reports on menstrual function in the DES-exposed female. In 1975, Herbst et al found no difference in menstrual histories between 110 DES-exposed females and 82 selected control subjects.[21] Subse-

quently, Barnes published similar conclusions based on 218 DES-exposed and 158 control cases. Both studies were of the same population, the Boston participants in the DESAD Project.[37]

In contrast, a 1977 study by Bibbo found differences between the DES-exposed and placebo-exposed female. Irregular menses, predominantly oligomenorrhea, occurred in 18% of 229 DES-exposed females compared to only 10% of 136 placebo control cases.[38] This study and subsequent investigations by Herbst et al in 1980[39] and 1981[36] on the same group of women (born at The Chicago Lying-In Hospital in 1951 and 1952) continued to identify menstrual irregularity and shorter duration of menstrual flow in those exposed to DES. In a separate study, Cousins also observed a shorter duration of flow (4 days or less) in the DES-exposed group (47% of 70 compared to 20% of 64 matched control subjects).[40]

DES, however, has not been found to affect the age at menarche. Bibbo et al found the average age for menarche to be 12 ± 1.2 years for both the exposed and unexposed groups.[38] Similar findings were reported by Barnes et al.

Fertility

Reliable conclusions on the fertility of DES-exposed females cannot yet be made. Many recently have entered the reproductive years and in keeping with the national trend have delayed their first pregnancy. Bibbo et al described a significantly lower incidence of pregnancy in women exposed to DES (18%) as compared to those given a placebo (33%).[38] These differences were later substantiated by Herbst et al, who reported conception rates of 67% for the DES-exposed and 86% for the placebo group.[39] Analysis of this population suggests that DES offspring had a higher level of primary infertility (53 of 338) than control subjects (19 of 298).[36]

Barnes et al, however, found no disparity between the incidence of pregnancy in the DES-exposed progeny (47% of 618) and their sisters or matched controls (50% of 618). Furthermore, the number of pregnancies in each group was similar.[41] Cousins et al also found no difference in the incidence of pregnancy, gravidity, and infertility between DES-exposed and matched control cases.[40] The male partner and other factors that may contribute to the infertility found in DES-exposed females require further investigation.

Pregnancy Outcome

Unfavorable pregnancy outcome such as premature birth, ectopic pregnancy, and nonviable birth is found more commonly in DES-exposed females.[31,36,39–42] The DESAD Project, studying 220 DES-exposed and 224 control subjects who had at least one pregnancy other than an elective abortion, demonstrated an increase in the relative risk for miscarriage (statistically significant), ectopic pregnancy, premature birth, and stillbirth.[41]

Herbst et al compared first pregnancy outcomes for DES-exposed and unexposed women and found an adverse outcome in 31% of DES-exposed compared to 8% of controls.[39] The incidence of premature births with first pregnancies was higher in the DES-exposed group (20% of 114) than in the placebo-exposed group (6% of 128). First trimester and midtrimester pregnancy loss also occurred in a higher portion of the DES-exposed women's first pregnancies. A significant percentage of DES-exposed women (7%) had ectopic pregnancy; eccyesis was not discovered in the control group.[36]

Barnes et al did not detect a statistically significant increase in poor pregnancy outcome in DES females with cervicovaginal structural defects (33% of 36 cases) compared to those without anatomic abnormalities (39% of 184 cases).[41] Herbst et al reported a significant increase in adverse first pregnancy outcome in those with cervicovaginal ridges (43% of 35 cases compared to 17% of 46 patients without ridges).[36] Cousins et al noted a greater incidence of premature delivery for DES-exposed females with gross cervicovaginal changes (71% of 7, whereas only 23% of 13 DES-exposed women without these changes gave birth prematurely).[40] However, because the number of women with such defects in each of these studies was small, it remains unclear whether DES-exposed females with cervicovaginal structural defects are more vulnerable to adverse pregnancy outcome. Furthermore, cervicovaginal ridges are not

stable anomalies and their influence on pregnancy outcome may vary with the extent of these changes.

Although current data suggest that there may be an increased risk for unfavorable pregnancy outcome among DES-exposed females with an abnormal hysterosalpingogram, these findings have not been correlated with any specific adverse pregnancy outcome. Thus, routine hysterographic evaluation of DES-exposed women appears unwarranted. The indications for hysterosalpingograhy should be similar for DES-exposed women and unexposed women undergoing infertility evaluation.

Although reproductive performance in DES progeny is associated with an increase in unfavorable outcome, approximately 82% of DES subjects have delivered at least one liveborn infant.[39,41] Although attentive prenatal care cannot prevent spontaneous abortion or ectopic pregnancy, it may avert midtrimester and late pregnancy losses.

Sporadic case reports and publications that describe several successful pregnancies in DES-exposed women after cerclage[36,43,44] suggest that cervical incompetence may be a factor. Frequent pelvic examinations, therefore, are recommended after the 16th week of gestation. Premature cervical effacement and dilatation in the absence of contractions or infection may be managed with cervical cerclage, particularly when there is a history of midtrimester loss. This procedure is justified only for traditional obstetic indications. Premature delivery can be recurrent, so close surveillance is advisable in subsequent pregnancies.

Embryology

Although details of the development of the human lower genital tract remain uncertain, it generally is believed that the paired müllerian ducts appear by the sixth week of gestation, advance in a caudal direction toward the midline to the urogenital sinus, and fuse cranially by the eighth week to form the uterovaginal canal. The vaginal portion of this epithelial tube (lined by columnar epithelium) is replaced cranially by the vaginal plate. Proliferation of the epithelium enlarges the plate. Canalization of this solid epithelial plate occurs cranially by 18 weeks to form a stratified squamous lining.

Exposure of the fetus to synthetic estrogens may interfere with the transformation of vaginal columnar epithelium into squamous epithelium or hamper the growth of the vaginal plate. These changes in development would result in a shorter plate which would lead to the squamocolumnar junction developing caudally either at the periphery of the cervix or in the vagina.[45]

Conclusion

Ironically, a drug introduced in the 1940s for use during pregnancy to prevent adverse reproductive outcome has since been associated with structural malformations of the genital tract and an increase in pregnancy loss, prematurity, and ectopic pregnancy in those women who were exposed in utero. Reproductive dysfunction may be even more pronounced in the subgroup of DES-exposed females who have anatomic abnormalities.

Although adenocarcinoma was the first major complication attributed to antenatal DES exposure, the risk is low. Although the incidence of clear cell adenocarcinoma in DES-exposed females declines after the age of 20, the prevalence of this malignancy in older women of the pre-DES era suggests future risk for DES progeny.

The incidence of squamous intraepithelial neoplasia in DES-exposed women exceeds that of clear cell adenocarcinoma. However, data are not available to indicate that squamous cell carcinoma in DES-exposed women will be more frequent than in the unexposed. Other adverse consequences may become evident with continued follow-up of those mothers who took DES during pregnancy, as well as females and males exposed to the drug in utero.

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13 Dysmenorrhea and Premenstrual Syndrome

Christine L. Cook

Dysmenorrhea

Painful menstruation or dysmenorrhea is the most common medical disorder occurring in adolescent females. The recurrent crampy lower abdominal pain experienced by many young women is usually accompanied by one or more nonspecific complaints. These include nausea, vomiting, diarrhea, headaches, and muscle cramps. Although considerable attention has been focused on the psychosocial aspects of this process, work during the last two decades has shifted the emphasis toward physiologic changes. The important role of prostaglandins (PG) in the pathophysiology of this condition and the value of the prostaglandin synthetase inhibitors (PGSI) in the treatment of dysmenorrhea have been elucidated.

Prevalence

In a large survey of young women, Klein and Litt found that 1611 of 2699 (60%) menarchal adolescents reported dysmenorrhea. Fourteen percent of these females frequently missed school because of this difficulty.[1] A slightly higher prevalence (72%) was noted in a Scandinavian survey in which only 19-year-olds were studied. Similarly, 15% of these women limited their activity during menstruation.[2]

The American survey identified increasing prevalence with progressive chronologic and gynecologic age, as well as sexual maturity. The occurrence of dysmenorrhea was slightly lower among patients with low socioeconomic status (SES). Race did not correlate with prevalence of dysmenorrhea; however, school absenteeism was significantly higher in each SES group among blacks compared to whites.[1]

Premenarchal instruction has not been shown to reduce the likelihood of dysmenorrhea.[1] However, there is a correlation between the presence of maternal or sibling menstrual pain and its occurrence in adolescents.[2]

The method of contraception is a determinant of dysmenorrhea in adolescents as well as older women. Oral contraceptives are associated with approximately a 60% reduction in incidence,[3] whereas an intrauterine device (IUD) will increase the incidence.[4]

Finally, the prior occurrence of a viable pregnancy will reduce the prevalence of dysmenorrhea. On the other hand, women who have had pregnancies terminated either by spontaneous or induced abortions have the same prevalence as nulliparous individuals.[2]

Pathophysiology

Adolescents experiencing painful menstruation are most likely to have primary dysmenorrhea. This condition is characterized by onset soon after menarche as ovulation is established and menstrual bleeding becomes cyclic. Usually presenting within a year of the first episode of vaginal bleeding, primary dysmenorrhea is not associated with any identifiable pathology of the reproductive system.

On the other hand, a marked increase in menstrual discomfort after a period of regular menstruation or the appearance of menstrual

pain in a previously unaffected woman is consistent with secondary dysmenorrhea. One of several pathologic states may lead to this condition. These include endometriosis, pelvic inflammatory disease, pelvic congestion, congenital malformations of the müllerian system, cervical stenosis, adenomyosis, or uterine leiomyomata, polyps, or adhesions. In addition, the presence of an IUD may precipitate dysmenorrhea.

Primary dysmenorrhea is associated with several abnormalities of uterine activity. There is an elevation of basal uterine tone to greater than 10 mmHg.[5] The active pressure within the uterus is also increased, while the frequency of uterine contractions rises to more than five per 10 minutes. Uterine blood flow is thus reduced causing ischemia and pain.[6]

There is strong evidence that endogenous PG play a major role in this process. In 1957 Pickles first reported the presence of a "menstrual stimulant" extracted from menstrual blood which caused smooth muscle contractions.[7] He subsequently demonstrated that the active stimulant was a prostaglandin.[8] Endometrial $PGF_{2\alpha}$ levels are higher in the secretory than the proliferative phase and greater in ovulatory than anovulatory patients.[9,10] A significant increase in the concentration of $PGF_{2\alpha}$ in the endometrium of dysmenorrheic patients compared to amenorrheic patients has also been noted.[11] Furthermore, a greater total secretion (in a 2-hour period) of $PGF_{2\alpha}$ occurs in the menstrual flow of women with dysmenorrhea.[12] Although the cause of increased prostaglandin secretion in primary dysmenorrhea is not known, steroid hormones have been shown to affect PG production. Tsang and Ooi have demonstrated the in vitro ability of hormones to control $PGF_{2\alpha}$ secretion from endometrial tissue.[13] They found that progesterone markedly inhibited $PGF_{2\alpha}$ secretion by proliferative but not secretory endometrium. 17β-Estradiol increased $PGF_{2\alpha}$ secretion in tissue from both phases of the menstrual cycle.

Primate work has demonstrated an estrogen-induced drop in progesterone during the luteal phase, mirrored by a rise in $PGF_{2\alpha}$.[14] In a comprehensive review of new concepts of dysmenorrhea, Ylikorkala and Dawood summarized additional evidence for a role of PG in menstrual pain.[15]

Prostaglandin Synthetase Inhibitor Treatment

The important role of PG in the etiology of dysmenorrhea has been greatly supported by the demonstration of a reduction in menstrual pain among women treated with prostaglandin synthetase inhibitors also termed nonsteroidal antinflammatory drugs (NSAID). Although the quality of NSAID treatment trials has been hampered by the subjective nature of patient descriptions of pain, as well as other methodologic problems,[16] a significant response of dysmenorrhea to NSAID therapy does occur in many women.

Several groups of NSAID have been studied for their effect on dysmenorrhea. These include benzoic acid derivatives (aspirin), butyrophenones (phenylbutazone), indoleacetic acid derivatives (indomethacin), fenamates (mefenamic acid, flufenamic acid), and arylpropionic acid derivatives (ibuprofen, naproxen, ketoprofen).

Conflicting reports exist with respect to the efficacy of aspirin in relieving dysmenorrhea. Rosenwaks et al performed a double-blind crossover study of 32 dysmenorrheic women, comparing the analgesic efficacy of aspirin, naproxen sodium, and placebo.[17] Naproxen sodium afforded significant pain relief when compared to aspirin or a placebo. Aspirin was not superior to the placebo in reducing dysmenorrhea. In addition to subjective criteria for pain relief, a $PGF_{2\alpha}$ metabolite (PGFM) was measured pre- and posttreatment. Again, naproxen sodium significantly reduced PGFM compared to aspirin or placebo. However, using these objective criteria, aspirin suppressed PGFM levels significantly compared to placebo. With the use of a menstrual distress questionnaire (MDQ), Klein et al compared aspirin to a placebo. In contrast to the Rosenwaks study, MDQ scores were significantly lower with the use of aspirin, 600 mg four times a day. School absenteeism was also reduced in the aspirin-treated group.[18]

Both phenylbutazone[19] and indomethacin[20] have been evaluated in single drug studies. Relief of dysmenorrhea is high, but side effects with both drugs are also significant. Several double-blind crossover studies using indomethacin and placebo have been reviewed by Dingfelder.[21] In each case relief of dysmenorrhea was noted in approximately 75% of

patients, but a persistently high incidence of side effects was also reported.

Flufenamic and mefenamic acids have also been used for the treatment of dysmenorrhea. Double-blind crossover trials involving NSAID and a placebo have demonstrated significant relief of menstrual pain. Mefenamic acid, 250 mg four times a day, significantly reduced pain, nausea, and "weakness-dizziness," but not diarrhea, in the drug-treated group. Mild gastrointestinal side effects were reported by both drug- and placebo-treated women.[22] In a similar study, flufenamic acid, 200 mg three times daily, provided significant pain relief in 82% of patients. Vomiting and diarrhea were reduced in 66% and 52% of patients, respectively. Relief of each symptom was significantly greater than in the placebo group. None of the women in this trial withdrew due to drug-related side effects.[23]

The arylpropionic acid derivatives have been evaluated for the treatment of dysmenorrhea in a large number of single- and double-blind crossover studies.[16] Chan et al have shown that naproxen sodium, 275 mg three times a day, significantly reduced total menstrual blood loss as well as menstrual $PGF_{2\alpha}$ and PGE_2.[24] Relief of dysmenorrheic symptoms was also greater on this regimen compared to a control group and placebo-treated group.[24] Thirty trials in which naproxen sodium and ibuprofen were compared to each other, another NSAID or a placebo have been summarized by Owen.[16] She found that pain relief occurred, on the average, in 62% of women receiving naproxen and in 70% of women treated with ibuprofen. In both cases, approximately 20% of patients experienced slight or no pain relief, while the placebo response averaged 16%. Infrequent, minor side effects were reported, GI-related for ibuprofen, and CNS-related for naproxen.

Oral Contraceptive Agents

Ovulation suppression is another frequently employed, commonly successful approach to pain relief in primary dysmenorrhea. For the young patient seeking contraception who chooses birth control pills, ovulatory suppression is usually accompanied by relief of menstrual symptoms. Menstrual fluid prostaglandin is reduced below normal levels in women on oral contraceptives.[25] At least 90% will experience relief of primary dysmenorrhea.[26]

Future Treatment

An additional therapeutic alternative is currently being tested. Ulmsten et al have demonstrated in vivo and in vitro suppression of uterine contractions with the administration of the calcium antagonists, nifedipine and nicardipine.[27] Spontaneous contractions in myometrial strips from pregnant and nonpregnant patients were reduced. Furthermore, contractions induced by vasopressin, prostaglandin, and oxytocin were suppressed. Inhibition of uterine contractions was also demonstrated in women with severe dysmenorrhea.[27]

For the patient who fails to respond to NSAID therapy or ovulatory suppression, diagnoses other than primary dysmenorrhea must be considered. (See Chapter 6.)

Secondary Dysmenorrhea

The gynecologic history and pelvic examination will often suggest a pathologic etiology for dysmenorrhea. Recurrent episodes of pelvic inflammatory disease, irregular vaginal bleeding, or a delayed onset of pain associated with cyclic bleeding are important clues. Various laboratory tests may be instructive, e.g., complete blood count, erythrocyte sedimentation rate, and genital cultures. Imaging with ultrasonography or hysterosalpingography can be used to augment visualization when pelvic lesions are suspected. Finally, diagnostic laparoscopy, possibly accompanied by hysteroscopy, may be necessary to establish the diagnosis.

Even when the history and examination appear normal, the patient who has been unresponsive to NSAID therapy should be considered as a candidate for a complete evaluation as outlined above, including diagnostic laparoscopy.

Generally, secondary dysmenorrhea is best eradicated by specific treatment of the pathologic cause. However, certain benign pelvic conditions associated with increased PG synthesis may be approached with NSAID therapy. Pain attributed to uterine leiomyomata,

endometriosis, or the presence of an IUD may be ameliorated by NSAID. An added benefit in the case of IUDs and possibly leiomyomata is the demonstrated reduction in total menstrual blood loss for these women. Therapeutic regimens successful in the treatment of primary dysmenorrhea are effective.[28,29]

Adolescent dysmenorrhea is a very common cause of physical discomfort and psychosocial disruption. Careful attention to history and examination is essential in establishing an accurate diagnosis. This diagnosis is crucial to the institution of appropriate therapy. Successful response to modern therapeutic regimens can be expected in most young women.

Premenstrual Syndrome

Considerable attention recently has focused on a nonspecific constellation of symptoms that often presents cyclically. First described by Frank in 1931,[30] this pattern of physical and emotional changes was named premenstrual syndrome (PMS) by Katharina Dalton in 1953.[31] With increasing frequency, health care professionals hear female patients describe difficult days in the mid- or late menstrual cycle. They complain of fluid retention, bloating, breast tenderness, headaches, irritability, fatigue, anxiety, hostility, and/or depression. A craving for sweets (especially chocolate), salty foods, or alcohol is common. Often the patient says, "I feel like I am a different person just before my period," or "My life seems entirely out of control for several days each month."

Prevalence

Although the premenstrual syndrome may have always existed in some form, the reporting of it has dramatically increased in the past decade. Twenty to 40% of menstruating women have symptoms that interfere with their daily activities to some degree, while approximately twice that number will notice some physical or emotional alterations in the premenstruum.[32,33] Hargrove and Abraham specifically identified the incidence of symptoms in adolescents.[32] Eighteen percent of 13- to 15-year-old girls had significant PMS-type complaints, and 31% of older teenagers had similar symptoms. The incidence among other women of reproductive age was 40 to 60%.

Diagnosis

Currently there are no universally accepted objective criteria for confirming the diagnosis of PMS. However, daily recordings of the previously mentioned symptoms through two or three complete menstrual cycles are useful in selecting the woman whose physical and emotional changes fit the usual PMS pattern. Although Ruble[34] has shown the increased tendency to incorrectly report physical symptoms as being premenstrual, there is no diagnostic option. Reviews of patient diaries reveal several possible presentations. Most women have PMS symptoms for the 7 to 10 days prior to menstruation. A smaller group of patients will have their most severe problems at midcycle, with lesser complaints during the luteal phase; variations exist. Of primary importance in a correct diagnosis is a symptom-free period shortly after menstruation.

Abraham has encouraged separating patients according to the clustering of certain symptoms.[35] The PMT-A patient has anxiety, irritability, and nervous tension beginning at midcycle and processing to the time of menstruation. PMT-H women have weight gain, abdominal bloating and tenderness, breast congestion and mastalgia, and peripheral edema. A premenstrual increase in appetite and a craving for sweets characterize PMT-C women. Shortly after eating large amounts of refined sugar, these women have headaches, palpitations, fatigue, and fainting spells. PMT-D patients suffer from premenstrual depression, withdrawal, and occasional suicide attempts. They usually are referred by psychiatrists. Initial psychiatric care often is sought only after pressure from family or friends. These women have difficulty talking about their problems and self-awareness further is complicated by lethargy, confusion, and incoherence. An increase in the incidence of suicide during the premenstruum has also been reported.[36] Because of extensive crossover between groups, many physicians do not find these categories particularly helpful.

Pathophysiology

An abnormality of various end organ responses to the hormone shifts of the menstrual cycle appears to occur in PMS. Although many theories have been proposed, it remains unclear why some women, both physically and emotionally, tolerate these physiologic changes whereas others do not.

Hormones

Progesterone and estrogen abnormalities were postulated in Frank's[30] original work on PMS, which stated that women with PMS had insufficient progesterone and an excess of estrogen. Other researchers have agreed,[37,38] but the theory has not been proven. Several authors have demonstrated normal luteal function in women with PMS. Basal body temperature graphs, endometrial biopsies, and sex steroid levels are unchanged.[39–41] Furthermore, improved surveillance of PMS patients has shown that complaints often are most severe when progesterone levels fall.[31,42]

Fluid Retention

Fluid retention often is considered an important factor that predisposes women to PMS. Sodium retention caused by ovarian steroids has been considered crucial in the initiation of PMS symptoms.[43] However, estrogen has only a slight and transient effect on sodium and water retention in normal women.[44] Daily administration of progesterone causes an increase in circulating aldosterone levels within 2 to 3 days. There is a luteal phase increase in aldosterone that has been blamed for the symptoms associated with the fluid retention found in many PMS patients.[45] However, repetitive premenstrual weight gain in significant amounts is uncommon and no correlation has been established between the fluid retention and the severity of other symptoms.[46,47] Retained fluid in some PMS women, rather than a primary event, may represent one more end organ effect of a central neuroendocrine process. Local responses may explain some of the PMS symptoms that appear to result from local edema but are not associated with an increase in total body water. Abdominal pain and bloating, mastalgia, and headaches in the premenstruum have all been attributed to localized fluid shifts.[48]

Prostaglandins

The prostaglandins' (PG) role in dysmenorrhea is now widely accepted, and PG also have been implicated in the premenstrual syndrome. Many of the peripheral effects associated with PG occur in PMS patients, including diarrhea, nausea and vomiting, dizziness, headaches, depression, and hot flushes. The primary evidence in support of the PG theory comes from the good response found in some patients treated with prostaglandin synthetase inhibitors NSAID.[49,50] Although the placebo effect is strong in trials using these medications (and in other forms of PMS therapy), several NSAID have reduced most PMS symptoms. Moreover, PGE_2, $PGF_{2\alpha}$, and a PGF metabolite are all significantly lower in PMS patients treated with a PGSI.[51]

A deficiency in pyridoxine (vitamin B_6) also is being considered in the pathophysiology of PMS. Vitamin B_6 acts as a coenzyme in the biosynthesis of dopamine and serotonin. For this reason, Abraham suggested that an inadequate supply of vitamin B_6 increased susceptibility to stress.[35] Certain prostaglandins also depend on vitamin B_6 for the conversion of dietary essential fatty acids (specifically linoleic acid) to gamma-linoleic acid (GLA), which then is converted to PGE_1.

Prolactin

Attention also has focused on a possible excess of prolactin in women with PMS. The osmoregulatory role of prolactin in a number of vertebrate species is well known. Behavioral effects in animals, including changes in parenting and migratory behavior, have been reported.[52] In the human, psychotropic drugs modify prolactin secretion. However, there is no direct evidence that prolactin alters mood. Conflicting reports exist concerning luteal phase prolactin levels in PMS. Some authors have found no change,[53] whereas others have demonstrated an increase in serum prolactin associated with PMS symptoms.[54]

Endogenous Hormone Allergy

Mabray et al have suggested that an allergic response to endogenous progesterone may account for PMS and "other menstrual disorders."[55] In a prospective single-blind study, progesterone neutralization therapy was used.

Each patient determined her own end point. Twenty-eight of 29 women had complete or marked relief from PMS. Conclusions regarding the efficacy of this treatment must be withheld until other investigators attempt hormone desensitization with PMS patients.

Hypoglycemia

Oral glucose tolerance curves are flattened with delayed hypoglycemia in the luteal phase. Morton et al believe this could account for the PMS sufferer's headaches and cravings for sweets.[56] Unfortunately, PMS usually is not relieved simply by eating, nor do all women with documented hypoglycemia have PMS.

Endogeous Opiate Peptides

Reid and Yen recently suggested that progesterone increases central endogenous opiate peptide (EOP) activity.[57] PMS symptomatology may be caused by the abrupt withdrawal of high levels of EOP in the midluteal phase. A much smaller progesterone rise occurs at midcycle. However, an unusual degree of sensitivity to withdrawal would explain why some women have PMS symptoms 2 weeks prior to menstruation.

Support for this theory comes from primate and human studies. In the rhesus monkey, direct measurement of β-endorphin concentrations in the portal-hypophyseal blood demonstrated high levels of EOP in the midluteal phase with very low levels at menstruation. In humans, administration of naloxone, the opiate receptor antagonist, suggests a role for EOP inhibition of gonadotropin release.[58] In the luteal phase, naloxone administration results in high titers of serum LH. Usually gonadotropins are low at this time. In contrast, administration during the follicular phase causes no change in the LH level, suggesting that EOP inhibition of gonadotropin release is minimal at this time.

In one study, the administration of naloxone did not improve PMS symptoms.[59] In fact, women given the placebo had a significantly greater reduction in stress. The EOP withdrawal symptoms that Reid and Yen discuss[48] may have been initiated in the naloxone trial by allowing hyperfunction of previously suppressed dopaminergic functions and raising stress levels. In addition, naloxone is a short-acting antagonist and may have lasted only long enough to produce initial withdrawal symptoms, but not long enough for the long-range effects of reduced endorphin action to occur.

The midluteal phase PMS symptoms—fatigue, depression, food cravings, and constipation—may result from increased EOP activity that is associated with a low release of norepinephrine or dopamine. When EOP inhibition ceases, the rebound hyperactivity of these pathways could result in the late luteal phase complaints of irritability, anxiety, tension, aggression, and diarrhea.

Management

The most consistent observation made by professionals who treat PMS v ctims is the initial relief felt by almost all these women when they finally know their concerns are being taken seriously, there is a physiologic explanation, the problem is quite common, and they are not going crazy. Often this combination of understanding and being understood sufficiently reduces the vicious cycle of stress and anxiety, enabling a woman to learn to tolerate the difficult days. Communication with others who have PMS also seems helpful. Nevertheless, there are PMS patients who need additional aid. Because the pathophysiology of the syndrome is not clearly understood, pharmacologic regimes generally have been unsatisfactory. Still, many have been used in response to the various theories on the etiology of PMS.

Hormones

More than 40 years ago Gray reported on the successful treatment of 35 of 38 women with intramuscular progesterone.[40] In one case, he reported using the patient as her own control with a placebo that had only a very transient ameliorative effect. Various doses of progesterone were used depending upon the severity of the symptoms. Since then, many investigators have reported on synthetic progestins and progesterone. Dalton's work in England with progesterone has received considerable attention. She believes that the failure of patients with the premenstrual syndrome to respond to progesterone treatment is either because they've been incorrectly diagnosed or

the frequency of dosage has been incorrect.[60] However, a double-blind crossover study using progesterone and a placebo failed to identify a difference in response,[61] nor has there been consistent improvement with trials of synthetic progestogens, androgens, estrogens, or oral contraceptives.[62]

Diuretics

Although excessive fluid retention has not been found in most women with PMS and the severity of PMS symptoms has not been shown to correlate well with total body water retention, a number of physicians have attempted to treat PMS with diuretics. O'Brien has reviewed uncontrolled studies where diuretics have been used to treat PMS.[63] Several of these trials suggested improvement. O'Brien carried out a double-blind, placebo-controlled study of spironolactone, administering 25 mg four times daily in the luteal phase. Eighteen patients showed a significant improvement in mood assessment scores and weight reduction on this regimen.[63] However, double-blind studies done by Mattson and van Schoultz[64] and Reeves et al[65] did not substantiate these results.

Vitamin B_6

PMS's response to vitamin B_6 therapy is variable. Uncontrolled studies generally have been encouraging. However, Stokes and Mendels did not confirm these findings in a controlled study.[66] On the other hand, Abraham and Hargrove reported that 500 mg of vitamin B_6 taken daily for three consecutive menstrual cycles resulted in a significant improvement in symtpoms that was in excess of the placebo effect.[67] In addition, Mattes and Martin,[68] in a 6-month, double-blind, multiple crossover study, found 50 mg of pyridoxine daily to be more effective than a placebo in reducing PMS symptoms.

Bromocriptine

Andersch has reviewed 14 placebo-controlled studies that used bromocriptine for the treatment of PMS. He concluded that there is no substantial support that bromocriptine is an effective drug in the treatment of premenstrual syndrome and that symptoms such as irritability, depression, and anxiety were not significantly improved.[69] The only consistently improved symptom was mastodynia.[70] The administration of 2.5 mg twice daily was required for a good response.

Danazol

The antigonadotropin danazol also has been used to treat PMS. Suppressing the hormonal changes of the menstrual cycle might be expected to also suppress PMS symptoms. Unfortunately, most authors report consistent improvement only in breast discomfort.[71,72] However, Labrum reports "dramatic relief" in 25 of 30 women treated with 10 to 50 mg daily in an uncontrolled trial.[33] It is Labrum's opinion that the antiestrogenic effect of danazol could cause a relative suppression of serotonin secretion in the luteal phase, which could reduce the intensity of the withdrawal effect in the premenstruum.

Essential Fatty Acids

At the 1983 International Symposium on Premenstrual Tension and Dysmenorrhea, Horrobin and Brush reported the use of gamma-linoleic acid (GLA) in PMS treatment.[73] Although no follicular/luteal phase differences were found in the essential fatty acids and their metabolites, a significant elevation of linoleic acid with a significant reduction in GLA and all subsequent metabolites was noted. They summarized the results of double-blind, placebo-controlled studies at the Universities of Dundee, Wales, and Helsinki, and noted that women treated in these centers had a significant improvement of the full range of PMS symptoms when treated with GLA. He suggested that women with PMS may have a minor defect in the metabolism of essential fatty acids.

The Future

If further studies confirm the importance of excessive exposure to EOP in the etiology of PMS, narcotic antagonists may be useful. Clonidine, an α_2-adrenergic agonist, might be used to prevent withdrawal symptoms. Recent success in the detoxification of addicts is encouraging.

Finally, the availability of gonadotropin releasing hormone (GnRH) agonists would provide an agent that could consistently suppress cyclic hormonal variation and the asso-

ciated changes in EOP activity which Reid and Yen have implicated in this disorder.[57]

Frustration is inevitable when an objective diagnosis is not possible and consistently effective therapy has not been identified. For the adolescent suffering from PMS, the possibility of many years of unpleasant cyclic physical and emotional changes may be frightening. As there is no way to accurately predict which patients will benefit most from behavioral, pharmacologic, nutritional, or hormonal therapy, the value of understanding and patient education cannot be overemphasized.

Moreover, careful surveillance of the literature for the results of work now in progress is important for the health care provider who treats PMS victims of any age.

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Endocrine Disturbances of Puberty 14

Alvin F. Goldfarb

Female psychosexual maturation is the culmination of events that express themselves through puberty, menarche, and nubility. It is the purpose of this chapter to review the endocrine abnormalities of puberty. To do this, a review of intrauterine pituitary-ovarian function, the normal mechanism of puberty, and clinical problems of sexual precocity and delayed sexual maturation will be presented.

Intrauterine Life

During fetal and neonatal life, the hypothalamic-pituitary-gonadal axis becomes capable of hormone secretion and also develops the neuroendocrine mechanisms for their regulation.[1] In addition to the immediate implications of sexual differentiation, this represents the first step in a continuing developmental process that leads to puberty. A derangement in this process may lead to sexual infantilism, precocious puberty, and even disorders of fertility or sexual behavior in adults.

After reestablishing the diploid number of chromosomes, the earliest sign of sexually dimorphic development is the appearance of fetal ovaries. This does not occur histologically until about 10 to 12 weeks of fetal age, and it is not until 24 weeks that typical multilayered primary follicles are seen. Prior to this time, the interstitial cells are the only ovarian cells with ultrastructural features suggesting possible steroidogenic potential. Although biochemical differentiation of the ovary, as reflected in its ability to convert 19-carbon steroids to estrogens, may begin as early as that of the testes, it does not appear that the fetal ovary makes an appreciable contribution to the concentration of circulating sex steroids. In vitro studies indicate that the fetal ovary synthesizes small amounts of progesterone, dehydroepiandrosterone, androstenedione, estrone, and estradiol. These steroids may play a role in the regulation of ovarian germ cell multiplication and atresia.

Pituitary Gonadotroins

The temporal pattern of fetal pituitary gonadotropin secretion is very different from that of human chorionic gonadotropin. Serum concentrations of FSH and LH are low or undetectable before 10 weeks of gestation; they peak at 16 to 18 weeks, and then decline. During the second trimester, serum FSH and LH concentrations in female fetuses are considerably higher than in males. At midpregnancy, values in female fetuses reach the adult castrate range, whereas those in males rarely attain even the normal adult range. Fetal serum levels of pituitary gonadotropins decline in both sexes in the latter half of pregnancy.

Gonadal Response

The fetal ovary appears responsive to FSH stimulation but is relatively deficient in LH chorionic gonadotropin receptors. There is some evidence that ovarian follicular development may be arrested in the absence of

normal pituitary function. The temporal relationship between ovarian development and fetal serum gonadotropin concentration has been described by Winter et al.[1] FSH and LH first appear in the circulation when primordial germ cells differentiate into oocytes and granulosa cells begin to proliferate. As gonadotropin levels decline in the latter half of pregnancy, there is a remarkable loss of germ cells through atresia, suggesting that local gonadotropin-dependent steroid secretion plays a role in the preservation of ovarian follicles.

Neonatal Changes in the Reproductive Endocrine Process

By birth, the reproductive endocrine system is structurally complete, but the mechanisms that regulate gonadotropin secretion continue to mature throughout childhood and adolescence. Serum concentrations of FSH and LH are low in both sexes, but the newborn pituitary responds to gonadotropin releasing hormone (GnRH) stimulation.[2] The disappearance of placental estrogens and progesterone from the circulation elicits a brisk increase in pituitary gonadotropin secretion in all infants, beginning toward the end of the first week. In males serum FSH and LH concentrations peak at 1 to 2 months of age and then decline to the normal prepubertal range by about 4 months.

Fetal β-Endorphins

Rasmussen et al used a 23- to 24-week fetal mediobasal hypothalamus in an in vitro perfusion system to demonstrate that a pulse injection of naloxone, an opiate receptor antagonist, could elicit an acute increase in GnRH release within 30 minutes.[3] Constant infusion of naloxone (1 hour) induced a sustained increase in GnRH release, which was promptly inhibited by a pulse of β-endorphin administered halfway during the nalaxone infusion. These studies demonstrate that endogenous opiates have an inhibiting effect on GnRH release from the human fetal mediobasal hypothalamus.

In female infants, serum FSH and LH concentrations continue to rise until about 3 months, at which time FSH levels may be as high as those in the postmenopausal woman. At this time, gonadotropin secretion is not only pulsatile but also shows rhythmic fluctuations reminiscent of those of early puberty. Mean serum FSH and LH levels subsequently decline slowly to reach a preadolescent nadir around age 2 to 3. This neonatal gonadotropin rise elicits only a slight ovarian response as shown by an increase in the number of large follicles, a variable rise in serum estradiol and 17-α-hydroxyprogesterone, and occasional breast enlargement.

This postnatal surge in gonadotropin production appears to be initiated by removal of the inhibitory influence of placental steroids. The difference in the magnitude and duration of the increase in males presumably reflects the influence of testicular androgens, because neonatal castration of the male monkey results in an exaggeration of the usual gonadotropin rise.[4] This feedback effect on androgens also is reflected in the gonadotropin response of infants to GnRH stimulation. Although no sex difference is seen at birth, within a few weeks the FSH response of female infants becomes greatly exaggerated and exceeds that seen in infant boys or older girls.

However, there is increasing evidence that the subsequent decline in gonadotropin levels is a result of active neural inhibition of GnRH secretion and not feedback inhibition by gonadal steroids, because it also occurs in agonadal infants. The neuroendocrine mechanism for prepubertal suppression of gonadotropin secretion has not been elucidated, although its final expression appears to be a reduction in GnRH secretion.[5] Already, it is possible to consider new approaches using GnRH or its analogs for disorders such as precocious puberty and hypogonadotrophic hypogonadism. In addition, clinicians are now beginning to recognize that abnormalities of pituitary or gonadal function during the neonatal period significantly affect later reproductive function.

Physiology of Puberty

Reproductive function is the ultimate consequence of the physical, physiologic, and hormonal events that begin in intrauterine life and culminate in pubescence. In the United States, the average age of onset of puberty is

between 8 and 13 in girls and between 9 and 14 in boys. In some worldwide studies, the age of pubertal onset is 6 to 12 months later. Kaplan and Grumbach have proposed that the hypothalamic-pituitary-gonadal unit is functional during fetal life and early infancy and is suppressed to a low level during childhood.[5] They also imply that all components exclusive of the central nervous system (CNS) such as the pituitary gland, gonads, and sex hormone target tissue may be activated precociously by administering the appropriate hormone and have no more than a minor role in the suppression of puberty. The interval between infancy and pubertal onset may be regarded as a state of functional GnRH insufficiency that is terminated by reactivation of augmented and pulsatile GnRH secretion.

In normal and agonadal children aged 4 through 11, it has been suggested that an intrinsic CNS inhibitory mechanism develops that suppresses the release of pulsatile GnRH. The interaction of these two components—an intrinsic CNS inhibitory mechanism that suppresses pulsatile release and a highly sensitive tonic negative feedback mechanism—would decrease gonadotropin secretion in the prepubertal child. The rise in basal levels and pituitary gonadotropin reserve after age 11 therefore reflects a lessening of the CNS inhibitory restraint and decreased negative feedback, with a concurrent increase in GnRH secretion and pituitary responsiveness. The precise nature of the postulated intrinsic inhibitory restraint to GnRH release and the onset of puberty has not been clarified. Some important factors may be reviewed, which include changes in neuronal activity and sensitivity to neuroamine synthesis and release, changes in opioid secretion, and melatonin synthesis and release.

The administration of a bolus of GnRH elicits several different patterns, depending upon the age of the person. Prepubertal children have a minimal but significant rise in LH after GnRH administration. Some increase in LH response to GnRH may be elicited in the peripubertal period before any physical evidence of secondary sexual development, but a marked increase in LH response to GnRH is seen in the pubertal child. In the adult, the LH response to GnRH is augmented. Thus, the increase in pituitary LH reserve and sensitivity to GnRH is the hallmark of puberty. In contrast, FSH shows sex-specific change but no maturational alteration in response to GnRH. Prepubertal and pubertal females release significantly more FSH in response to GnRH than do males.

Enhanced secretion during sleep is another maturational change first seen in the peripubertal and pubertal periods.[6] EEG changes during sleep may be correlated with oscillations of LH. The demonstration of sleep-associated enhanced LH secretion in agonadal patients during puberty indicates that this process is not dependent on gonadal function, but rather is a maturational expression of changes in the CNS and the hypothalamic control of LH release. Support for this hypothesis can be found by administering hourly individual pulses of GnRH, which activate the pituitary gonadotropin—gonadal axis in immature prepubertal rhesus monkeys. The administration of 500 μg of GnRH for 14 days to patients with hypothalamic hypogonadism leads to an increase in LH and FSH response to GnRH.

A late maturational phase of gonadotropin secretion is the development of the cyclic release of gonadotropins or the positive feedback mechanism. The cyclic pattern is best exemplified by the hormonal changes that occur during the menstrual cycle. This effect cannot be induced in prepubertal or early pubertal girls. Despite circulating estradiol levels similar to those during the follicular phase, no rise in LH can be induced.

Adrenarche

The onset of adrenarche in man and chimpanzee occurs about 2 years before hypothalamic pituitary gonadotropin maturation.[7] Plasma concentrations of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) rise progressively in both males and females from the ages of 7 or 8 until 13 to 15. The growth of pubic and axillary hair has been attributed to the secretion of other adrenal androgens and sex steroids during puberty. A temporal relationship is apparent between histologic changes in the adrenal cortex, i.e., the differentiation in growth of zona reticularis, and the rise in DHEA-S production of adrenarche.

The onset of adrenarche before the activa-

tion of gonadal function had led to the hypothesis that adrenal androgens may facilitate the onset of puberty and the maturation of the hypothalamic-pituitary-gonadal unit. However, many studies do not support this. Premature adrenarche (onset of pubic or axillary hair growth) before age 8 is not associated with the abnormal advancement of gonadal function. Adrenarche occurs in the absence of gonadal function in persons who have hypergonadotrophic hypogonadism and in those with isolated gonadotropin deficiency. Adolescents with Addison's disease have pubertal onset and the growth spurt at the normal age. These findings are consistent with the existence of separate control mechanisms for adrenarche and gonadarche.

Weight

Frisch and Revell's work on the role of body mass and composition in growth and menarche is well known. It is apparent that under the influence of central nervous system development, adrenarche, and adequate nutrition that includes a weight of approximately 47 kg with 13% body fat, menarche should occur in 95% of girls by the time they are 12.9 years old.[8]

Normal Progression of Puberty

The progression of puberty is slow and consistent and is best illustrated in Table 14-1. In discussing problems of sexual maturation, it is best to use the Tanner classification as indicated in Table 14-2. This allows us to communicate in a meaningful fashion concerning female pubescence and to see that normal pubescence begins in the neonate and continues through the development of menarche and ovulation.

Table 14-1. Mean Onset of Female Pubertal Changes in the United States.

Age	Characteristics
9–10	Beginning of height spurt
	Growth of bony pelvis
	Female contour fat deposition
	Budding of nipple
10–11	Budding of breasts
	Appearance of pubic hair (may precede breast budding in 10%)
11–12	Appearance of vaginal secretions
	Growth of internal and external genitalia
	Increase in vaginal glycogen content; lowering of pH
12–13	Pigmentation of areolae
	Growth of breast
13–14	Appearance of axillary hair
	Increase in amount of pubic hair
	Acne (in 75–90%)
	Menarche
15–16	Arrest of skeletal growth

Table 14-2. Tanner Classification of Female Adolescent Development.

Stage	Breast	Pubic Hair
I	Papillae elevated, preadolescent	None
II	Breasts and papillae, small mounds	Sparse, long, slightly pigmented
III	Breasts and areolae confluent, elevated	Darker, coarser, curly
IV	Areolae and papillae projected above breast	Adult type—pubis only
V	Papillae projected, mature	Lateral distribution

Precocious Puberty

Sexual precocity is any sign of secondary sexual maturation at an age more than 2.5 standard deviations below the mean. In girls, secondary sexual development before 8 is precocious and worth evaluating. Complete isosexual precocity or true precocious puberty is the result of premature maturation of the hypothalamic-pituitary-ovarian axis. Because the process of maturational development is normal, normal menses occurs. Incomplete isosexual precocity occurs if gonadotropin output or the secretion of sex steroids is independent of pituitary gonadotropin stimulation; feminization will occur, but ovulation will not. Heterosexual precocious puberty is maturational changes that are inappropriate for the person's sex, either virilization in the female or feminization in the male (Table 14-3).

Precocious puberty is associated with accelerated growth. Accelerated osseous maturation also occurs, ultimately resulting in short stature, although the sexually precocious person may be the tallest and heaviest of his or

Table 14-3. Differential Diagnosis of Precocious Puberty.

I. Complete, true precocious puberty
A. Idiopathic or constitutional
B. Neurogenic, cerebral lesions
1. Tumors of hypothalamus, pineal, or cortex including hamartoma, craniopharyngioma, glioma
2. Infections, including toxoplasmosis, encephalitis, meningitis
3. Neurocutaneous syndromes, neurofibromatosis
4. Developmental defects, including microcephaly, tuberous sclerosis, aqueduct stenosis, craniostenosis
5. Trauma
6. Miscellaneoue: Sturge-Weber syndrome, diffuse encephalopathy, idiopathic epilepsy
C. McCune-Albright syndrome
D. Juvenile primary hypothyroidism
E. Silber syndrome (craniofacial disproportion, small stature, retarded bone age, increased gonadotropin levels)
II. Incomplete or pseudoprecocious puberty
A. Premature pubarche
B. Premature thelarche
C. Adrenal lesions: congenital adrenal hyperplasia, Cushing's syndrome, tumors
D. Ovarian tumors: estrogen-producing, granulosa-theca cell, luteoma
E. Iatrogenic: androgen or estrogen administration, vitamins, oral contraceptives
III. Extrapituitary gonadotropin production
A. Gonadotropin-secreting tumors: choriocarcinoma, teratoma, hepatoblastoma, dysgerminoma
B. Exogenous gonadotropin administration

her peers. Fifty percent of sexually precocious girls do not reach an adult height of 5 feet, although early interruption and treatment may enable some to grow more. Prior to epiphyseal closure, these children always are larger than their peers, but intellectual and psychosexual development is appropriate for their age.

Premature Thelarche

Unilateral or bilateral breast development without other signs of sexual maturation, i.e., sexual hair or growth of the labia and uterus, is not uncommon in infancy and childhood. Referred to as premature thelarche, it usually is seen before age 2 and may be due to the relative increase in gonadotropin output during this time, which stimulates a responsive ovary to produce estradiol.

Premature thelarche rarely is found after age 4; in the older child it may be the first sign of impending precocious puberty. Plasma estrogens may be slightly elevated for age but usually are low and transient. Nipple development ordinarily is absent, and growth of the vaginal mucosa is uncommon. Ordinarily, breast enlargement regresses after a few months, although occasionally it may be persistent. Although the cause is uncertain, transient episodes of estrogen secretion or possibly even the estrogen contained in the follicular fluid of an ovarian cyst can be responsible. Premature thelarche is by definition benign, and progressive sexual development and accelerated growth and bone maturation do not occur.

Premature Pubarche or Precocious Adrenarche

Premature pubarche refers to the isolated appearance of pubic hair (and rarely axillary hair) before the age of 8, with no other signs of sexual maturation or virilization. More common in older but still prepubertal children, it can occur in infancy. Pubarche is the first sign of adolescence in 20% of normal girls older than 8; differentiating normal pubarche from premature pubarche is difficult. Circulating levels of adrenal androgens, including DHEA, DHEA-S, androstenedione (Δ_4A) and testosterone (T), are increased for age but appropriate for the stage of sexual hair growth. Although this increase in adrenal output may reflect the effect of estradiol upon adrenal steroidogenesis, possibly through inhibition of the 3β-hydroxysteroid dehydrogenase enzyme complex, this has not been completely proven. Premature adrenarche is a nonprogressive disorder that is compatible with normal secondary sexual maturation later on. Bone age and height age may be slightly advanced for chronologic age; some patients have had abnormal EEGs without neurologic findings.

Iatrogenic Sexual Precocity

Prepubertal children are extremely sensitive to exogenous sex steroids, and unusual sources of androgens or estrogens may induce a significant response. Some sex hormones still

may be found in vitamin preparations, tonic lotions, and creams. These agents were once more readily available and were a common cause of sexual precocity. Even today, precocious sexual development occurs as a result of oral contraceptives.

Heterosexual Precocious Puberty

Virilization in a girl usually indicates significant organic disease, the most common of which is congenital adrenal hyperplasia as a result of 21-hydroxylase or 11-hydroxylase deficiency. Clitoromegaly, short stature, frequent hirsutism, and acne are the common clinical findings. Rarely, an ovarian or adrenal androgen-producing tumor can cause virilization. 3β-hydroxysteroid dehydrogenase deficiency is a rare type of congenital adrenal hyperplasia that is characterized by elevated DHEA and DHEA-S and an extremely low secretion of aldosterone and cortisol. Most of those severely affected die in infancy. Female heterosexual precocious puberty requires a diligent search for the secretion of androgens from a virilizing tumor or hyperplasia.

Diagnosis of Sexual Precocity

The first step in the investigation of a child with precocious sexual development is to identify potential life-threatening disorders, particularly a neoplasm of the central nervous system, ovary, or adrenal, or ectopic chorionic tissue. Ordinarily, no serious cause is discovered. The next priority is to determine if over time there is evidence of progressive pubertal change or whether the process is self-limited.

The first step involves taking a detailed history that may reveal symptoms suggestive of intercurrent disease, perinatal abnormalities or injuries, previous infection, ingestion of sex steroids, or similar conditions in family members. Information is needed regarding headache or other neurologic symptoms, exposure to medications, and any vaginal bleeding. The developmental history of the girl is important, including measurements that can be plotted on a growth chart to determine the onset of increase in height, the velocity, and degree of correlation between height and weight measurements.

The physical examination should detail the degree and synchrony of secondary sexual development and the appearance of acne, facial and body hair, axillary gland development, body odor, muscular development, and galactorrhea. Neurologic examination is essential, with assessment of visual fields and optic discs. The evaluation of skin lesions, in reference to McCune-Albright syndrome or neurofibromatosis, also is important. An examination also should be carried out for abdominal, gonadal, or adnexal masses, or coexisting endocrine disease.

The vagina should be examined as well as determination made of uterine size. The adnexa should be evaluated for masses. Examination under anesthesia may be necessary when evaluating a resistant child, but a great deal of information can be found by simply observing vaginal mucosa, labia minora, vaginal cells in a wet mount, and by a rectal exam. It is important to observe whether estrogenization has occurred.

Radiologic examination is important both to rule out intracranial disease and to assess bone age. Sex steroids accelerate osseous maturation. In addition, intracranial calcification of the McCune-Albright syndrome may be observed. Serial bone age determinations may be helpful as a guide to the rate of pubertal progression. Pneumoencephalography or carotid arteriography should be done only when there is other evidence of CNS lesions. Computed tomographic (CT) scans may be useful in the diagnosis of small tumors within or adjacent to the hypothalamus.

Further laboratory evaluation includes an assessment of circulating FSH and LH values, testosterone, and estradiol, and other measurements indicated by history and/or physical examination. The measurement of DHEA-S and/or DHEA may be valuable, or a 17-hydroxyprogesterone determination may indicate congenital adrenal hyperplasia. Thyroid function tests (thyroid stimulating hormone) may be important to rule out severe primary hypothyroidism that may be associated with accelerated sexual maturation and galactorrhea. The latter also requires serum prolactin. Ordinarily, those parameters measured for true precocious puberty agree with the bone age and not the person's chronologic age. However, in sexual precocity that results

from tumor hormone production, gonadotropin levels are depressed by the sex steroids.

Endocrine Evaluation in True Precocious Puberty

The evaluation of true precocious puberty from the endocrinologic standpoint must include a study of estrogens, androgens, and gonadotropins. Estrogens can be evaluated by serum estradiol and vaginal smear. As in normal puberty, girls with idiopathic precocious puberty show estradiol levels that vary greatly. This leads to two considerations: repeated evaluation of the patient increases the chance of finding high levels of estradiol, and transitory secretory peaks are sufficient to saturate target cell receptors for a period that is adequate to induce and maintain the signs of estrogenicity.

There may be particular features of the receptors or of sex hormone binding globulins that play an important role in these events. The different behaviors of estrone and estradiol seem to suggest that maturation in precocious puberty mainly involves the hypothalamic-pituitary-gonadal axis whose activity is shown by transient estradiol increases.

Often, studying a vaginal smear for maturation index may be the simplest way to identify the levels of serum estradiol. If one visualizes only parabasal cells on a vaginal smear, it can be assured that the serum estradiol levels are below 10 pg/ml. When showing only superficial cells with complete estrogenization of the canal, the vaginal smear indicates that the estradiol levels are above 100 pg/ml. There usually is no correlation between secondary sexual characteristics and estrogen levels; however, a relationship exists between constant stimulation over the time that the person is exposed to estrogens and the development of secondary sexual characteristics.

Dihydrotesterone (DHT) and Δ_4A levels seem higher in girls who have precocious puberty than in those of the same chronologic age, while DHEA and DHEA-S show significant differences between cases. The variability of adrenal function, which already is remarkable in normal puberty, is even more so in idiopathic precocious puberty. This indicates that the maturation of the hypothalamic-pituitary-gonadal axis is not closely linked to that of the hypothalamic-pituitary-adrenal axis.

The behavior of gonadotropins has been assessed under basal conditions after GnRH stimulation during sleep. Various studies have found higher average basal levels of LH and FSH in those with true precocious puberty than in prepubertally normal girls.[9,10] However, gonadotropin response to GnRH may be an indicator of true precocious puberty. Still, the response should be monitored continuously. In monitoring response to GnRH, one can then note a trend toward the pubertal type of LH response to GnRH.

Treatment of Precocious Puberty

Finding a specific etiology to precocious puberty is the key to its management. Isosexual idiopathic precocious puberty, however, is most common, so attempts must be made to suppress gonadotropin secretion. The most important goal is to cease ovulatory menses and, if possible, regress any sexual development. Rapid intervention is indicated if menarche has occurred, or if the child is at risk for significant psychologic trauma.

Unfortunately, treatment that suppresses menses and secondary sexual development does very little to increase the ultimate height of the child. Medroxyprogesterone acetate (MPA), 100–200 mg intramuscularly weekly or biweekly, may be administered; menses and further breast enlargement will cease, but patients are likely to be short because there is no effect on the rate of growth and bone maturation. The drug has side effects, which include the suppression of adrenal cortical function; MPA itself has some glucocorticoid function and will substitute for the suppressed adrenal activity. In addition, weight gain and a possible acceleration of diabetes mellitus in predisposed persons have been reported.

Other agents proposed for therapy have included danazol, a 2,3-isoxazol derivative of 17-ethinyltestosterone, an impeded androgen with some progestational effects.[11,12] Although it stops menses and inhibits further breast development, danazol does not seem to benefit ultimate height and can cause virilization.[14] Cyproterone acetate, an antiandrogen,

has many of the advantages and disadvantages of MPA.

Children with precocious puberty have a physical appearance that belies their psychosexual and psychosocial maturation. Thus, many have severe psychologic disturbances, and are shy and withdrawn. Counseling often is helpful. Although these children tend to socialize with peers closer to their size and strength, their social skills are not as advanced, and problems can occur. Advanced school placement should be considered for those with the intellectual capabilities, and early sex education may be indicated.

A few years ago cyproterone acetate replaced medroxyprogesterone for the treatment of true idiopathic precocious puberty. This drug was introduced 20 years ago as a progestin; its feminization of male rat fetuses was discovered during toxicity tests. This led to the discovery of the following antiandrogenic effects: (1) it competes with testosterone at target tissue level; (2) it blocks testosterone and estrogen synthesis in the gonads; and (3) progestin activity prevents the increase in gonadotropins that usually occurs with a fall in plasma levels of testosterone. The third point is especially important because a purely antiandrogenic substance without any progestational activity would compete with androgens at a receptor level and might cause a compensatory increase in gonadotropin secretion, which would nullify the block of testosterone production.[12]

When to treat a female with precocity usually depends upon whether menarche was prior to age 8, there is progressive thelarche and pubarche, and bone age is at least 2 years greater than chronologic age but no older than 12. One can properly select patients for treatment by using these limits. Unfortunately, the primary drugs now available in the United States for the treatment of precocity is medroxyprogesterone acetate or danazol. Cyproterone acetate has not been FDA approved for treating precocity.

Delay of Puberty

Delayed puberty can best be defined as the absence of signs of pubertal development by 13.5 years or if menarche has not occurred within 4.5 years after the onset of breast development. Delayed pubertal development also may be present in a girl who does not menstruate by age 16 or whose height and/or weight is significantly lagging for her chronologic age. Rarely, anxiety alone is enough to warrant an examination.

The examination of a girl with delayed puberty should determine whether she will undergo spontaneous, albeit delayed, puberty, or if she has disorders that will lead to sexual infantilism and require treatment. The diagnosis should determine whether a patient has constitutional (idiopathic) delay, hypogonadotrophic hypogonadism, or primary gonadal failure with hypergonadotrophic hypogonadism (Table 14-4).

Constitutional Delayed Adolescence

Although delayed sexual and somatic development occurs in both sexes, this common condition is much more frequent in boys. These patients fail to show any signs of sexual development and because of an absence of sex hormones they grow at a slow preadolescent rate. Bone age is thus less than the chronologic age. Often these are children who are smaller than average throughout childhood, which

Table 14-4. Classifications of the Various Causes of Delayed Puberty in Girls.

	Site of Defect	Gonadotropin Levels	FSH/LH Response to GnRH	Estrogen Levels
Constitutional delay	Delayed maturation of hypothalamus	Low	Prepubertal	Low
Reversible hypogonadotropism Permanent hypogonadotropism	Hypothalamus or Pituitary	Low	Prepubertal or absent	Low
Hypogonadotropism related to increased androgens	Adrenal or ovary	Low	Prepubertal	Low
Hypergonadotrophic hypogonadism	Ovary	Raised	Accentuated	Low

suggests that all body tissues may be slow in maturing. This theory would agree with the idea that a certain level of general physical maturity must be attained before the hypothalamic-pituitary mechanism is activated. Sometimes the family history shows that one of the parents or other family members have had the same type of delayed development.

Once puberty has begun, these girls usually go through the normal stages, and sometimes overall adolescence appears somewhat accelerated. Prolonged delayed puberty may be noticed in combination with malnutrition, such as that found with anorexia nervosa, or systemic disease such as uncontrolled juvenile diabetes, hypothyroidism, or inflammatory bowel disease. Recently, we have seen several persons who have had delayed sexual maturation as a result of stress related to divorce. Attempts to use GnRH testing to differentiate constitutional delay of puberty from other forms of hypogonadotropism have not been successful[13-15] if the person with delayed maturation does not show any early signs of puberty.

Pubertal Development Without Menarche

Although this problem must be considered in a differential diagnosis of delayed puberty because of the absence of menarche, this is not true delayed puberty. Girls born with an imperforate hymen usually have normal pubertal development; but the menstral flow cannot be exteriorized. These patients can be easily diagnosed by observing a bulging hymen. In the Rokitansky syndrome, there is congenital atresia of the vagina and/or the uterus. Like the previous group, these girls can have normal pubertal development. However, there is no menstrual flow because of either an absent uterus or atresia of the vagina. This syndrome often is associated with renal anomalies.

Hypogonadotrophic-Hypogonadism

This group includes persons with tumors of the hypothalamic-pituitary axis, destructive disorders of this area of the brain, trauma, or congenital anomalies that may be associated with deficient secretion of FSH or LH.

Sometimes, several children in a family are affected, suggesting an autosomal recessive trait. More frequently, however, idiopathic hypopituitarism is the cause of delayed puberty. It can be either a panhypopituitarism where most or all of the pituitary hormones are deficient or an isolated gonadotropin deficiency. Growth hormone deficiency and its resulting short stature are an important part of the clinical picture of panhypopituitarism. In addition, a gonadotropin deficiency is diagnosed in these patients at the presumptive age of puberty. In contrast, the hypopituitarism, which involves only gonadotropin secretion, is not expected in a girl who has grown normally throughout childhood.

Several syndromes related to the abnormal development of parts of the central nervous system during fetal life also can adversely affect the development of the hypothalamus and pituitary. These syndromes include Kallmann's, Prader-Willi, and Laurence-Moon-Bardet-Biedl. Kallmann's syndrome is associated with hypoplasia of the mamillary and olfactory bodies as well as the hypothalamus. This pathogenesis also explains the anosmia found in these patients. Because the defect is at the level of the hypothalamus, it is understandable that the response of FSH and LH to GnRH administration is normal. Kallmann's syndrome appears to have a familial incidence and is believed to be an autosomal dominant trait.[16]

The Prader-Willi syndrome includes short stature that is often noted from birth, obesity in early infancy, and severe hypotonia improving with age. There are numerous other malformations, including a narrow forehead, strabismus, and relatively small hands and feet, that are particularly evident in the middle of childhood.[18] There also is some mental deficiency, and at puberty most of these patients have hypogonadotrophic hypogonadism. It has been suggested that the etiology of the syndrome is related to a defect of the midbrain. Recently, a study of karyotypes of patients with this syndrome has shown a small deletion of chromosome 15, which might be responsible for the abnormality.[8]

The Laurence-Moon-Bardet-Biedl syndrome is another poorly defined disorder that includes obesity, mental deficiency, polydactyly, and syndactyly. Early in childhood it is possible to note retinitis pigmentosa, which

later in life may result in partial or complete blindness. Finally, there usually is a marked general hypoplasia and at puberty a hypogonadotrophic hypogonadism.

Hypergonadotrophic-Hypogonadism

The defect in this group is a primary gonadal abnormality, which results in a lack of sex steroid secretion. In the absence of negative feedback, there is a large incremental gonadotropin ouput from the anterior pituitary. Classification of patients with hypergonadotrophic hypogonadism is based on study of the karyotype. One large group of patients will present with Turner's syndrome, the usual karyotype being 45,X. A second subset will have a 46,XX karyotype, while a third has 46,XX/45,X karyotype.

Turner's Syndrome

It is well known that these patients are phenotypic females with normal müllerian ducts but streak gonads. In addition to the short stature and sexual infantilism that results from the absence of gonads, these patients have multiple somatic abnormalities, including webbing of the neck, various abnormalities of the face, and a broad chest, as well as congenital lymphedema, structural abnormalities of the kidney, and cardiovascular anomalies (particularly coarctation of the aorta).

In addition to the usual karyotype of 45,X, some patients may have mosaicism. Mosaic karyotype patients present fewer stigmata of Turner's syndrome. Moreover, their gonadal function may be variable, and they may even have normal menstruation.

Other variants are isochromosomes, the most frequent being isochromosome of the long arm of the X. These patients also have fewer stigmata of Turner's syndrome but present with short stature and sexual infantilism. The patients with an isochromosome of the short arm of the X-chromosome also have fewer stigmata; they have hypogonadism but are of normal height. The phenotypes of deletions of portions of the X-chromosome may be variable, depending upon the degree of chromosomal loss.

The pattern of gonadotropin secretion in Turner's syndrome is unusual. A rise in basal levels of FSH occurs shortly after birth and up to age 4. Between 4 and 10 the levels remain low and close to the range for normal prepubertal children.[17,18] Then the FSH levels increase again as expected in agonadal subjects.

Pure gonadal dysgenesis is associated with either a 46,XX or a 46,XY karyotype. The phenotype is entirely female with normal müllerian ducts and bilateral streak gonads. This is reminiscent of Turner's syndrome, although there usually are no associated stigmata of this syndrome and the stature is normal during childhood; the body proportions, however, may be eunuchoid in adulthood because of the absence of gondal hormones. Of interest is the finding that the 46,XX syndrome appears to be an autosomal recessive trait, whereas the 46,XY syndrome is an X-recessive trait or male-limited autosomal dominant. It has been suggested that the syndrome is related to early destruction of a gonadal analage. This results in the development of müllerian ducts and the presence of female external genitalia in both sexes. It must be noted that many variants of this syndrome have been reported where the gonadal dysgenesis is partial rather than complete, resulting in variable degrees of either androgen production in the 46,XY karyotype or estrogen secretion in the 46,XX subject.

True hermaphroditism is by definition the presence of well-differentiated testicular and ovarian elements in the same person. Although the karyotype of most true hermaphrodites is 46,XX, some have a 46,XY complement, and others are mosaic, 46,XX/46,XY. Testicular elements in these patients usually result in some degree of masculinization of the external genitalia. In addition, hypergonadotrophic hypogonadism at puberty occurs only in persons who have an insufficient amount of gonadal tissue.

Steroid enzyme deficiencies can be found with 46,XX hypergonadotrophic hypogonadism. These deficiencies may be either 20-hydroxylase, 22-hydroxylase, 3-β-hydroxysteroid dehydrogenase, or 17-hydroxylase. In the 46,XX karyotype, steroid enzyme deficiencies also may be at any of the above places. It must be noted that 46,XY patients with these enzyme deficiencies are unable to produce testosterone during fetal life and are born with a female phenotype.

The enzyme 17-hydroxylase is necessary for the formation of 17-hydroxyprogesterone. Persons with this deficiency have decreased cortisol and increased ACTH secretion. The increase in ACTH causes increased secretion of both corticosterone, which compensates for the low cortisol, and deoxycorticosterone, the cause of hypertension in these patients. In addition, 17-hydroxylation of steroids is a necessary step in the formation of both androgens and estrogens. As a result, persons with 46,XY have female external genitalia and abdominal testes. No pubertal maturation takes place because of the inability to secrete testosterone. The 46,XX patients have normal female external and internal genitalia, but at puberty their ovaries are incapable of producing estrogen.

17,20-Desmolase is necessary for the formation of C-19 steroids from C-21 precursors. A deficiency of this enzyme will result in inability of the gonads to produce androgens or estrogens. Because the defect occurs during fetal life, 46,XY infants have a female phenotype. Both 46,XY and 46,XX patients at puberty have hypergonadotrophic hypogonadism.

Complete androgen insensitivity in a person with 46,XY results in a female phenotype and feminization at puberty, despite plasma androgens that are within or above the normal ranges for adult males. These patients often consult a physician because of primary amenorrhea. They are taller than normal. It has been shown that this disorder is the result of an abnormality of the androgen receptor in the target cells. Moreover, this trait is X-linked recessive. The serum levels of LH usually are consistently above normal, while FSH levels often are raised, suggesting an impairment of the negative feedback mechanism.

Evaluating Delayed Puberty

Except for genital malformations that prohibit menstrual flow in females with secondary sexual characteristics, delayed puberty appears to reflect changes in gonadotropin secretion.

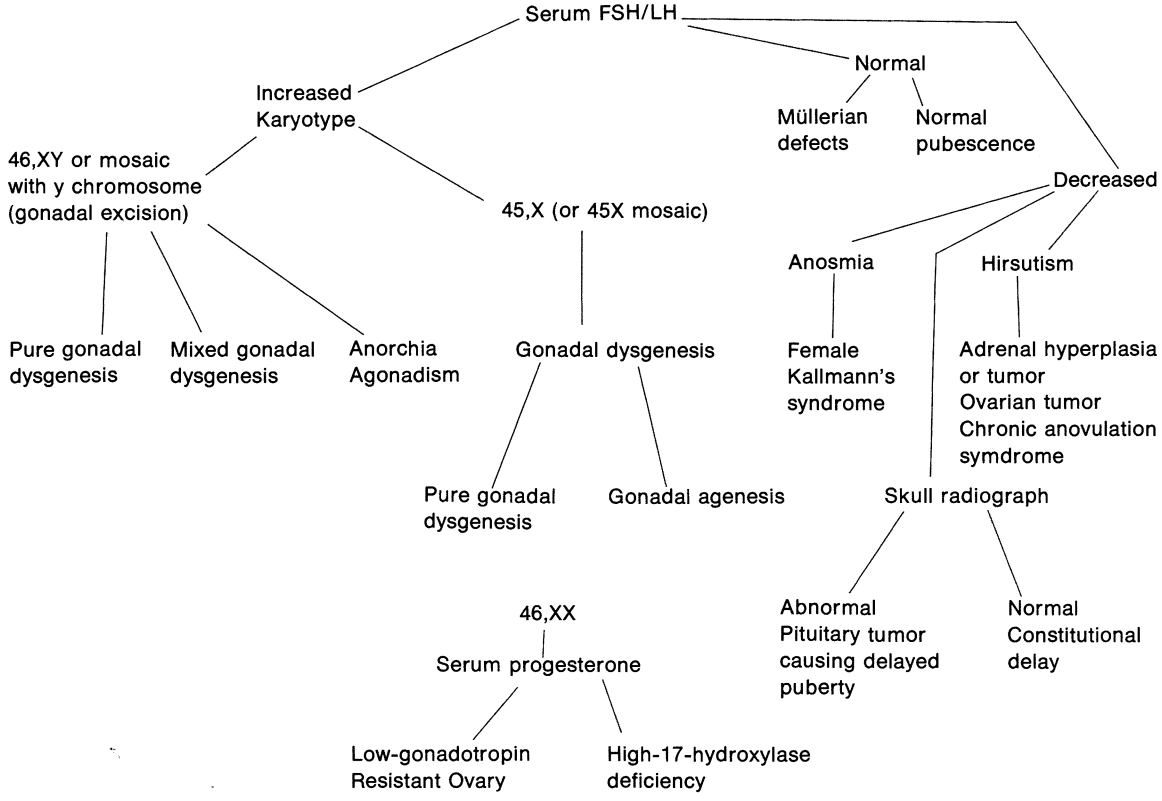

Figure 14-1. Evaluation of Delayed Puberty.

Figure 14-1 details the evaluation and determination of delayed puberty.

After determining the gonadotropins, it is important to immediately obtain a chromosome analysis if the patient is hypergonadotrophic. Depending upon whether the karyotype is 46,X, 46,XX, or 46,XY, several syndromes need to be considered. On the other hand, if there is hypogonadotropism, the most frequent cause will be constitutional delay. Before establishing this diagnosis, however, it is necessary to rule out several other possibilities. A history of systemic disease and malnutrition suggest reversible hypogonadotropism. Physical symptoms of virilization and laboratory confirmation of increased androgen levels will suggest possible androgen-producing tumors or syndromes. Neurologic symptoms along with a history of increased intracranial pressure and abnormal vision demand a CT examination of the sella turcica to diagnose the destructive process of the pituitary or hypothalamus. Deficiency of pituitary hormones (TSH, ACTH, GH) suggests the possibility of idiopathic hypopituitariam. Constitutional delay of puberty is established only when these other abnormalities have been ruled out.

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Anorexia Nervosa 15

John D. Looff and Emery Wilson

First recognized more than three centuries ago, anorexia nervosa is a syndrome combining unusual food-related behavior, the vigorous pursuit of thinness, and amenorrhea. Interest in this once little known syndrome has grown tremendously over the past several years, to the point that a national organization, the American Anorexia Nervosa Association, Inc., has been founded to aid patients and their families.[1] The illness seems to occur now with increasing frequency.[2] Recent studies in Great Britain have shown that in a middle-class population as many as one in 100 females age 16 to 18 may be affected.[3] The incidence varies between social classes and is more common in families whose fathers work in professional and managerial jobs.[4] Not limited solely to females, 5% of anorectics are males,[5] predominantly adolescents, although recent work describes a group of males at risk during middle age.[6]

The characteristics of the syndrome were first described by Sir William Gull more than 100 years ago and have changed very little.[7] The typical patient is an adolescent Caucasian girl under 25 who is in the middle to upper socioeconomic class, and has not had any apparent prior emotional or physical problems. Anorexia nervosa is particularly common in girls involved in ballet, fashion, modeling, sports, or other areas where physical appearance is important.[8] The syndrome begins when the person develops a distortion of body image and an excessive self-induced weight loss.[9] Unusual food-related behavior such as hiding food, spitting, and vomiting may occur.[10] As the girl continues to lose weight, amenorrhea occurs and, in fact, may be the presenting complaint.[11-13] It was this close association of weight loss with amenorrhea that led to earlier suggestions that anorexia nervosa was a form of pituitary failure.[14] More recent observation and endocrine assessment, however, suggest that the problem resides at the level of the hypothalamus. Whether this hypothalamic dysfunction is the primary problem or secondary to the weight loss is still unclear.

The precipitating factors of anorexia nervosa are variable and often difficult to differentiate from other symptoms of normal adolescence.[12,13,15] The literature has described deep-seated psychologic disturbances in the susceptible individual,[5] but the initiating mechanism is still unknown.[16] A complex interrelationship between psychologic abnormalities, hypothalamic dysfunction, and the effects of starvation is coupled with weight loss and amenorrhea and leads to anorexia nervosa.[5]

Signs and Symptoms

The first and most striking feature of the anorectic is usually emaciation.[3] Marked absence of subcutaneous fat accentuates the skeletal appearance, while the clothing may be designed to mask her body.[3] Other common features are seen in Table 12-1. Swelling of the ankles may be present and represents a more chronic feature usually accompanying severe starvation with electrolyte disturbances.[3]

Table 15-1. Symptoms and Signs of Anorexia Nervosa.

	Total No.	%	Reported in Starvation
Amenorrhea (22 postpubertal girls)	22/22	100	Yes
Constipation	26/42	61.9	Yes
Preoccupation with food	19/42	45.2	Yes
Abdominal pain	8/42	19	Yes
Intolerance to cold	8/42	19	Yes
Vomiting	5/42	4.9	No
Hypotension	36/42	85.7	Yes
Hypothermia	27/42	64.3	Yes
Dry skin	26/42	61.9	Yes
Lanugo-type hair	22/42	52.4	Yes
Bradycardia	11/42	26.2	Yes
Edema	11/42	26.2	Yes
Systolic murmur	6/42	14.3	No

From Warren MP: Anorexia nervosa. In Sciarra JJ (ed): Gynecology and Obstetrics. Philadelphia, Harper & Row, vol. 5, 1982, p 2.

Often the skin is rough and dry and accompanied by fine lanugo hair usually over the back and face.[3,13] The pulse rate generally is slow unless the person has recently eaten or binged, in which case it may be substantially increased.[3] Accompanying this induced metabolic state is a lowered blood pressure and a body temperature often below 96 F (35.6 C).[13] The extremities as a result generally are cold and often red or blue. The girl may be constipated and have abdominal pain.[13] Persons with anorexia nervosa are often fanatically preoccupied with food and may eat large amounts of low calorie foods while shunning carbohydrates.[13] Many anorectics are intolerant to cold; others may have periodic vomiting.[3] The majority of anorectics are restless, walking or standing whenever possible. In fact, the patient at the initial encounter may pace. Anorectics sleep less than others and often have a history of early morning activity.[3] Early in the disease the anorectic may increase her physical activity and exercise.[3] As the disease progresses, however, she may be so emaciated that her activity is severely limited.

Amenorrhea is a characteristic feature of anorexia nervosa and is often the symptom that causes the patient or family to seek medical advice.[9,16] Exceptions to this may include those who take hormonal contraceptives and binge eaters.[3] Anorectics with lowered body weight as a result of binge eating followed by vomiting have a higher metabolic rate often associated with the continuation of menstruation.[3] Seventy percent of patients cease to menstruate shortly after the onset of weight loss.[17,18] However, amenorrhea precedes the weight loss in 7–24% of anorectics.[17] It is unknown whether there exists some psychologic factor affecting menses prior to bizarre dieting or an independent hypothalamic abnormality.[16] However, evidence supports the theory that emotional disturbances affect menstrual function.[19,20] Studies of women in concentration camps have shown significant amenorrhea prior to any decrease in nutritional status.[21] Other studies of women entering religious life and nursing also showed a significant amount of amenorrhea.[22,23]

The degree of hypothalamic-pituitary-ovarian dysfunction and subsequent amenorrhea appears related to weight loss.[16] A high rate of weight loss has been observed in women with "postpill amenorrhea," with 75% underweight.[24] Five percent were anorectic and another 8% had anorectic traits.[24] Other studies in varied geographic populations have confirmed these findings.[25,26]

The menstrual abnormalities of ballet dancers have been extensively studied.[27,28] A delay in the onset of menses was observed, with the subsequent development of secondary amenorrhea in 15% and irregular cycles in 30%.[20] Only one-third reported normal

menses.[28] Dancers with menstrual abnormalities weighed significantly less than those menstruating regularly.[28] Other studies of dancers report a 28% incidence of amenorrhea. Again, those with amenorrhea were significantly underweight.[27]

Weight loss itself does not seem to determine menstrual function. Both the weight and percentage of body fat are reduced in female long-distance runners.[29] Moreover, 35% of female athletes are amenorrheic but do not weigh significantly less than control patients with regular menses.[30] Thus, weight loss is only one variable of regular menstrual function. These findings are consistent with the Frisch theory that states the onset and maintenance of menstrual function are dependent upon a minimum weight for height.[31] This minimum weight implies that a fat/lean or fat/body weight ratio exists for the maintenance of reproductive ability.[31] For menses to begin, fat must constitute an estimated 17% of body weight, while 23% body fat is needed for regular ovulation.[32] This ratio of body fat may be needed for extraovarian sources of estrogen to help support menstruation. Not all studies have supported these concepts, however.[33] Menses did not always resume following a return to normal weight or body fat. Amenorrhea, despite normal body weight, persisted in 10% of anorectics in one study.[34] Other studies have found amenorrhea in girls whose body fat was greater than 23%.[25] Clearly, this demonstrates the complexity of the problem. More than likely, a certain percentage of body fat is necessary but not totally sufficient for normal menstrual function.[32]

Basal metabolic rate may be another determinant in regular menstruation. Some people, in contrast to anorectics, lose weight by bulimia rather than food restriction. Bulimics have a higher basal metabolic rate at a corresponding weight than the true anorectic.[35] Consequently, return of menses occurs at a lower weight, most likely because of the increased basal metabolic rate.[35]

Fertility of anorectics has been studied little. Once weight has been restored and normal menstrual function resumed, no evidence of diminished fertility has been found. Several studies of anorectics have shown normal pregnancy rates with no increase in the rate of spontaneous abortion or maternal or perinatal morbidity.[15,36,37,38] Some patients have become pregnant without resuming menses[15] and one while still severely emaciated.[39] Although pregnancies usually proceed without problems, several patients have had their symptoms exacerbated by pregnancy.[16] Thus, anorectics should be discouraged from becoming pregnant until they have fully recovered. Fertility-inducing agents should be postponed until the patient's weight has been normal for 1 year and her eating habits and attitudes toward food have improved.[16] Oral contraceptives may be prescribed for sexually active anorectics but should be discouraged in amenorrheic girls who are not sexually active, because withdrawal bleeding may mask the return of normal menses and reinforce denial of the disease process.[16] The effects of a prolonged loss of estrogen (osteoporosis) are unknown.

Routine Laboratory Findings

As the severe starvation accompanying anorexia nervosa progresses, the body shuts down all but essential functions.[3] Reproductive potential and peripheral circulation are sacrificed to maintain a lowered metabolic rate.[3] Ten percent of the body's energy expenditure falls soon after the cessation of menstruation.[3] Further reduction in basal body temperature, pulse rate, and blood pressure are seen with progressive starvation.[3] Common laboratory findings are shown in Table 15-2. A hypoplastic bone marrow associated with petechia formation may be found.[13] Total white blood cell count may be reduced, with lymphocytes accounting for the majority of cells. In contrast to other forms of emaciation, anemia is rarely found.[9,13]

Other metabolic abnormalities reflect the dietetic pattern of the anorectic.[3] Serum lipid levels may be high or low depending on the amount of fat eaten, the frequency of eating, and the amount of carbohydrates in the diet.[3] Low levels of glucose with higher levels of insulin usually are seen with diabetic glucose tolerance tests.[3] Renal function generally is well maintained except in those who take diuretics and laxatives.[9,13] The resulting hypokalemia, if persistent, may result in long-term renal function impairment. The azotemia seen usually is the result of dehydration be-

Table 15-2. Clinical Laboratory Findings in Anorexia Nervosa.

	Total No.	%	Reported in Starvation
Abnormal electrocardiogram	13/25	52.2	Yes
Hypoplastic marrow	6/13	46.2	Yes
Blood urea nitrogen > 20	17/42	40.5	Yes
White blood cell count < 5000/mm^3	16/42	38.1	Yes
Relative lymphocytosis (> 49%)	6/42	14.3	Yes
Diabetic glucose tolerance test	6/16	37.5	Yes
Flat glucose tolerance test	4/16	25.0	Yes
Thrombocytopenia	1/4	25.0	No[a]
D-Xylose absorption	8/18	22.5	No[a]
Increased serum carotene	5/13	38.0	Yes
Hypomotile upper gastrointestinal tract	3/42	7.1	Yes
Anemia	3/42	7.1	Yes

[a]These parameters have not been studied in starvation.
From Warren MP: Anorexia nervosa. In Sciarra JJ (ed): Gynecology and Obstetrics. Philadelphia, Harper & Row, vol. 5, 1982, p 2.

cause creatinine levels are normal and correction of abnormal values occurs once therapy has been initiated. The selective carbohydrate avoidance and substitution of occasional binges of protein foods aggravate the azotemia.[3] The protein degradation products may exceed the kidney's excretion capacity.[3] Elevated serum carotene levels causing the skin to turn yellow—particularly on the palms—may occur after large amounts of raw yellow vegetables have been eaten.[3,9,13] Following the consumption of excessive fluids in an effort to curb hunger, edema may occur in dependent areas such as the ankles and pretibial regions.[3] Oddly, hypoalbuminemia usually is not seen.[9,13] Electrocardiogram abnormalities consist of low voltage with low, inverted waves which are possibly a reflection of lowered potassium levels.[9,13] A few subjects have been demonstrated radiographically to have hypomotility of the upper gastrointestinal tract. It is unknown whether this is due to an electrolyte or neurotransmitter abnormality.

Endocrine Abnormalities

Hypothalamic-Pituitary-Gonadal Axis

Studies of anorectics have demonstrated remarkably low levels of pituitary gonadotropins along with a marked estrogen deficiency.[13,40] The reduction of gonadotropins seems to correspond with reduced body weight[41-43] and appears more pronounced for luteinizing hormone (LH) than follicle stimulating hormone (FSH).[13,44,45] Some studies, however, have found no relationship between FSH levels and body weight.[42] In contrast to growth hormone, no relationship exists between baseline plasma LH and caloric intake or duration of amenorrhea.[42]

Studies of secretory patterns over a 24-hour period have shown a return of gonadotropins to prepubertal levels.[46,47] Those affected have either a low LH level during the 24 hours or a decreased LH secretory activity while awake and an increased LH level while sleeping.[47] These abnormal gonadotropin patterns exist in both anorectic and bulimic patients[48] and appear unique to this illness. Other types of amenorrhea such as gonadal dysgenesis,[49] menopause,[50] and polycystic ovary syndrome[51] fail to show this immature secretory pattern. Recently a patient with gonadal dysgenesis has shown this prepubertal LH secretory pattern.[52] However, she also had superimposed anorectic symptoms.

Studies of gonadotropin deficiency in anorectics have demonstrated abnormalities sug-

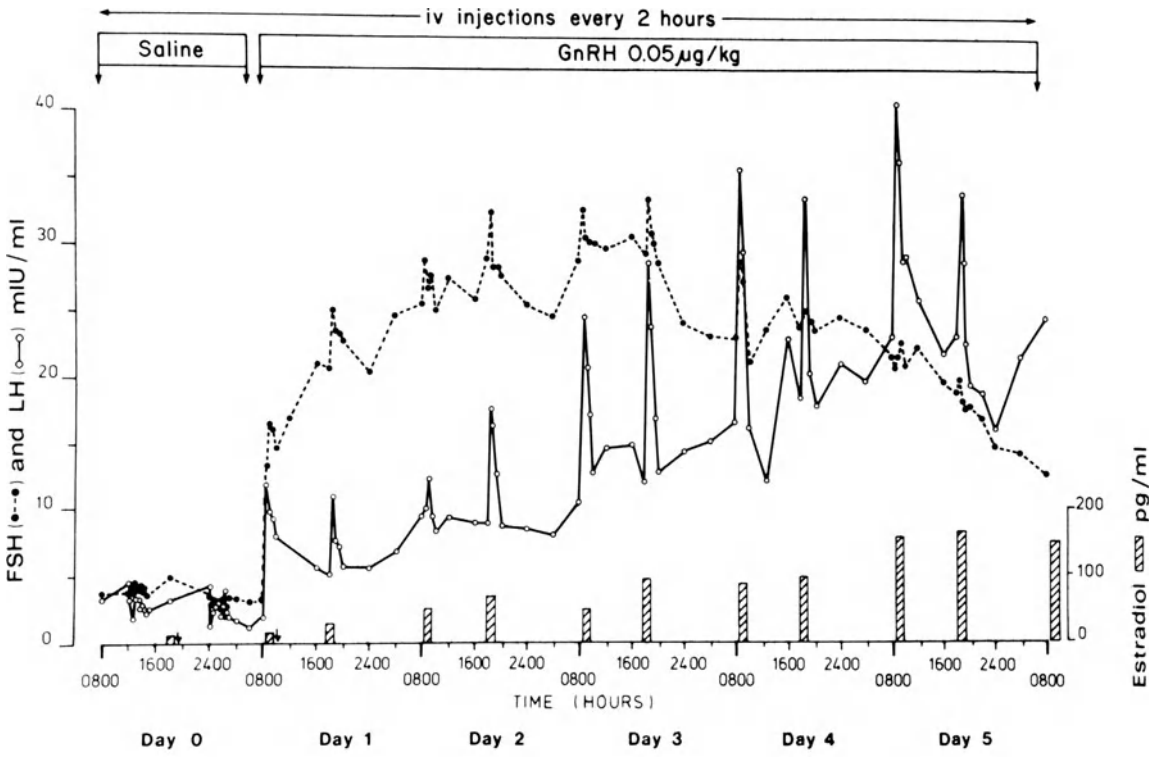

Figure 15-1. Plasma FSH (•), LH (○) and estradiol responses to intravenous GnRH (0.05 μg/kg) every 2 hours. From Marshall JC, Kelch RP: Low dose pulsatile gonadotropin-releasing hormone in anorexia nervosa: a model of human pubertal development. Journal of Clinical Endocrinology and Metabolism 49:712–18, 1979. Reproduced with permission.

gestive of hypothalamic dysfunction. The LH response to luteinizing hormone releasing hormone (LHRH) is greatly reduced.[53] The amount of this reduction appears directly correlated with the extent of weight loss; those with the greatest weight loss show the smallest response to LHRH.[41,54] Although this relationship also exists with LH, the FSH response to LHRH appears greater and more constant than that of LH even in severely underweight patients.[16] The return of LH responsiveness may be induced with repeated administration of LHRH.[54,55] Pretreatment with LHRH results in a progressive increase in LH response and a corresponding decrease in FSH secretion.[55] Eventually, the prepubertal response pattern returns to normal and with it a normal pattern of ovarian steroid secretion and follicular development.[55,56] This is seen in Fig. 15-1. The progressive rise in LH levels, the nocturnal increase in LH, and the progressive decline in FSH levels are demonstrated in this patient. These return-to-normal response patterns were established in a matter of days but illustrate well the normal pubertal maturation in females. The response appears greater and to occur earlier if pretreatment with LHRH is done by a sustained infusion rather than a single bolus.[44] Furthermore, the delay in response appears related to weight loss. In response to a 4-hour infusion of LHRH, those patients who were below 70% of normal body weight showed minimal responses in the first hour, while those with a higher weight revealed maximum levels of biphasic response after 4 hours.[42] Patients with weight loss and secondary amenorrhea without anorexia nervosa have had similar delays.[57]

Hypothalamic dysfunction responsible for the prepubertal gonadotropin response patterns is further supported by the response to clomiphene citrate. The LH response to clomiphene citrate is impaired in anorexia nervosa and causes LH release only in those who have regained their weight.[41,42] These results are not entirely unexpected. Clomi-

phene citrate acts by blocking the negative feedback of estrogen on hypothalamic releasing factors. Peripheral levels of estrogen are reduced in anorectics so that the hypothalamus already "views" lowered estrogen levels. Thus, further reduction by clomiphene citrate would not be expected to stimulate a gonadotropin surge.

As noted, these immature gonadotropin patterns appear to revert to normal once the patient achieves a body weight of greater than 80% of ideal.[58] FSH normalization appears to occur prior to the return of LH responses.[59,60] The persistence of an immature gonadotropin pattern has been seen in some patients who exhibited symptoms despite normal weight gain. The duration of illness, extent of weight loss, and percentage of body fat did not seem to be related to the degree of immaturity of gonadotropin secretion. However, once weight recovered, these patients demonstrated an adult LH pattern with no clinical symptoms.[48] Perhaps LH secretion is sensitive to continued psychologic stress or the unusual dietary factors that may alter neurotransmitter level of function.[16] In some subjects a hyperresponsiveness of LH and FSH to LHRH has been shown during weight gain.[61] These same patterns have been observed in children during early puberty and in other types of secondary amenorrhea.[62] Such observations suggest that a central nervous system (CNS) mechanism reverts and is responsible for the prepubertal pattern that somehow reverses during weight gain.[9]

Although not studied specifically in anorectics, the indoleamine pathway may affect gonadotropin release by decreasing LHRH responses. Serotonin may not affect gonadotropin release directly but is converted to melatonin in the pineal gland.[63] Melatonin itself appears to diminish the impact of LHRH in the pituitary and the action of peptide and sex hormones at their peripheral target organs.[63] Elevated serotonin levels have been found in anorectics[64] and this elevation may lead to increased prepubertal melatonin levels that, in turn, interfere with gonadotropin and hormonal function. Whether this represents an observed effect of anorexia rather than its cause is still speculative.

Estrogen levels are low in patients with anorexia nervosa.[13,4041] Although this is partially due to diminished gonadotropin secretion, studies suggest that estrogen metabolism appears altered. The metabolism of estrogen normally proceeds by 16-α-hydroxylation. During periods of weight loss this pathway becomes less active, while 2-hydroxylation is increased. This results in an increased formation of catecholestrogens (2-hydroxyestrone),[65] which essentially acts as an antiestrogen and have very low intrinsic estrogen activity.[66] These catecholestrogens may be responsible for buffering the effects of estrogen on the hypothalamic-pituitary system, thereby modulating gonadotropin release via a CNS mechanism.[67] In addition, the 2-hydroxylation pathway that appears to exhibit increased activity may itself play a role in gonadotropin release. It is speculated that 2-hydroxylated derivatives inhibit the metabolism of catecholamines by inhibiting catechol-*o*-methyl transferase,[68] an enzyme involved in the inactivation of norepinephrine and dopamine. By interfering with their inactivation, catecholestrogens potentiate the central action of catecholamines. The end result of a lowered estrogen level is further worsened by the lack of fat tissue, which may contribute extraovarian sources of estrogen to the peripheral pool.[9]

The response of LH secretion to estrogen feedback does not occur in anorectics prior to weight gain.[58] Following weight gain and the normal return of LH and FSH secretion patterns, the negative feedback effects of estrogen become apparent. The positive feedback effects, however, remain impaired longer in the majority of patients even though normal responses eventually occur.[58]

In summary, the above observations suggest a normalcy of the hypothalamic-pituitary-ovarian axis and responses once the patient has recovered from anorexia nervosa. As weight increases, so do basal levels of LH and FSH, with a return of normal adult patterns of secretion in response to LHRH. Often there may be an exaggerated response during this early weight gain. Concomitantly, the hypothalamus regains its responsiveness to the feedback effects of estrogen, which is initially negative feedback with a delayed response to positive feedback. With sufficient weight gain and the absence of clinical symptoms, the majority of patients regain normal menstrual function and fertility.

Adrenal

Studies of adrenal function in anorectics have detected elevated cortisol levels.[55,69,70] The normal circadian pattern is flattened or even reversed. Other studies have found a much higher level of preservation of the circadian rhythm in anorectics than in controls.[70] These changes may be caused by a number of mechanisms. As a result of a reduced metabolism, cortisol clearance is greatly reduced.[9,70] Similar findings are seen in victims of chronic malnutrition.[9] Moreover, despite normal values of cortisol-binding globulin (CBG), a decreased affinity of CBG for cortisol is present.[71] Previously, decreased cortisol binding in serum has been found in those with nutritional diseases such as kwashiorkor.[72] Other studies have suggested that production of cortisol is increased.[71] Indirect evidence suggests that the cortisol production rate is normally proportional to body size.[73] Although cortisol values were within the normal range, once corrected for body size, subjects' cortisol values increased. Studies of urinary steroid excretion generally have shown lowered values of 17-hydroxysteroids and 17-ketosteroids.[13,44] Suppression of adrenal activity was incomplete in a majority of patients,[73] although others responded normally to dexamethasone.[13] If suppression did occur, it was delayed in most cases. This is probably a reflection of the lowered metabolic clearance rate.[71] These high levels of cortisol suppress ACTH levels.[13] Furthermore, ACTH stimulation tests usually result in normal-to-hyperreactive adrenal responses,[13,74] suggesting that if a new circadian rhythm exists, a new set point has been determined by the hypothalamic-pituitary-adrenal axis to reflect these elevated cortisol levels.[9]

All changes in adrenal function in those with anorexia nervosa also have been described in starvation due to other causes;[16] however, cortisol production rate is thought to be reduced in malnutrition, in contrast to the higher level found in anorectics.[75] Adrenal function always returns to normal once the patient has gained an adequate amount of weight and is free of clinical symptoms.

Growth Hormone

Growth hormone (GH) levels are elevated in persons with anorexia nervosa,[55,76] just as they are in any form of starvation or fast that exceeds 12 to 15 hours.[9] Although basal levels are elevated, growth hormone levels usually respond normally to provocative stimuli.[9] The normalization of GH concentrations occurs with recovery.[41,44] Interestingly, the fall in GH occurs prior to any significant weight gain and seems related more to caloric intake.[44] Some studies have shown a drop in GH following a glucose load,[44,54] whereas others have noted a paradoxical rise;[70] this disparity may reflect the type of glucose solution used.[44,76] However, as overall nutrient status improves, this GH elevation does not occur.[76] This pattern is in contrast to LH patterns, which are related to the loss of body weight and are reversed by weight gain rather than caloric intake. A reduced growth hormone response in anorectics also has been reported in response to apomorphine,[54,76] but it returns to normal following weight gain.[76] Interestingly, the chronic use of apomorphine induces an anorectic state in normal persons.[77]

Fasting insulin levels also are variable—both lowered and elevated values have been reported.[78–80] Similar variability in insulin levels has been found in response to a glucose load.[44,54] A relative insulin resistance that seems to correlate with the severity of weight loss occurs with starvation and carbohydrate deprivation.[80–82] Despite normal glucose tolerance curves, insulin resistance also persists in anorectics after weight gain and in the absence of symptoms.[79,83] Other studies have found anorectics to have a relative insulin sensitivity.[84]

Thyroid Function

Serum concentrations of thyroxine (T_4) and triiodothyronine (T_3) are lower in patients with anorexia nervosa.[9] The lowered T_3 is associated with an increase in the inactive form of T_3.[85] In addition, hepatic uptake of T_4 and T_3 is decreased.[86] An explanation of these observations is that target tissues for thyroid hormones have regulatory mechanisms that are based upon metabolic needs. During periods of caloric deprivation and reduced metabolic activity, increases in calorigenic-conserving hormones such as inactive T_3 are favored. Thus, pathways involved in deiodination of T_4 would reduce production of active T_3 in favor of its inactive form. If similar

mechanisms exist at the pituitary, low T_3 concentrations might not be insufficient for the reduced metabolic needs, and thyroid stimulating hormone (TSH) would not increase.[87]

Indeed, TSH concentrations are normal in the majority of anorectics.[41,43,88] Response of TSH to thyrotropin releasing hormone (TRH) is normal but delayed from 30 to 120 minutes.[89] This delay in TRH response seems to be correlated with the degree of weight loss. Normal response occurs after weight is restored,[90] possibly reflecting an altered set point for pituitary thyrotropes.[9] Lowered T_4 and T_3 concentrations in the presence of a normal TSH concentration are not seen in hypothyroidism and cannot explain the amenorrhea associated with anorexia.

Prolactin

Increased prolactin secretion is the cause of secondary amenhorrhea in up to 25% of anorectics.[87,91] But despite attempts to determine if these abnormal levels are responsible for amenorrhea, studies consistently have revealed normal basal prolactin levels.[84,90,92] Normal prolactin responses following stimulation by TRH and dopamine blocking agents also are seen.[92-94] Anorectics, however, do not seem to have the sleep-induced rise in prolactin.[95] The low prolactin levels are thought a reflection of a suprahypophyseal influence, because normal prolactin responses can still be elicited by TRH.[16] Clearly, the amenorrhea seen in women with anorexia nervosa is not caused by abnormal prolactin secretion, nor is the failure to resume menstruation after weight restoration associated with elevated prolactin values.[16]

Antidiuretic Hormone

Persons with anorexia nervosa also may have clinical symptoms suggestive of mild diabetes insipidus.[80,84] An increased urine output is expected in anorectics because they drink a large quantity of liquids in lieu of food. The resulting increased urinary flow alters the concentration quotient to such a degree that renal capacity to concentrate urine is diminished. In addition, a relative protein deficiency may be seen, which impairs the kidney's concentration capacity further by lowering the area levels that maintain a concentration gradient.[1] In addition, anorectics have further abnormalities in water conservation. Antidiuretic hormone secretion is impaired, resulting in a failure to maximally concentrate urine.[80,84] Abnormalities in water conservation are closely related to those of thermoregulation.[80] Increases in urine concentration were seen in patients given exogenous vasopressin, confirming the diagnosis of partial diabetes insipidus.[84]

As noted, abnormalities of thermoregulation which are not related to a decrease of adipose tissue, but are suggestive of hypothalamic dysfunction, frequently are found in anorectics.[84] Failure to shiver normally as well as vasoconstriction occurs in response to cold, causing a fall in core temperature. Conversely, no vasodilation and minimal sweating occurs when heat and body temperature rise. The severity of heat intolerance appears closely correlated to the degree of weight loss.[80] This failure to regulate core temperature suggests abnormalities of thermosensitive centers in the anterior hypothalamus, motor centers for shivering in the posterior hypothalamus, or possibly abnormalities of centrally active neurotransmission.[9,80,84]

Neurotransmitters

It has long been known that neurotransmitters affect behavior and appetite.[96,97] Thus, neurotransmitters are implicated in the pathophysiology of anorexia nervosa. However, existing evidence is mostly indirect and speculation is varied. The insatiable appetite of anorectics has been thought to be the result of excess norepinephrine.[97] Moreover, those with anorexia usually are not depressed, as are persons with diminished norepinephrine levels. Consequently, adrenergic blocking agents have been suggested.[97] Other studies have found lower MHPG (3-methoxy-4-hydroxyphenylglycol) levels in anorectics.[98] A byproduct of norepinephrine metabolism, low MHPG levels reflect low norepinephrine values. Other indirect evidence suggests that increased dopamine levels may be responsible for anorexia.[96] Amphetamines, which release catecholamines, and apomorphine, a dopamine agonist, can produce an anorectic state and hyperactivity in normal individuals.[99] These symptoms may be reversed with a

dopamine blocking agent, which also results in a marked weight gain.[77] In contrast to these findings, other investigations have suggested a possible brain dopamine deficiency and advocate treatment with L-dopa.[100,101] Still other investigators have demonstrated an increased serotonin secretion.[64] Serotonin's interference with menstrual function has been discussed previously. The recent discovery of neuropeptides, particularly β-endorphin,[102,103] further supports the notion that anorexia nervosa is a result of hypothalamic dysfunction. Increased cerebrospinal fluid (CSF) opioid activity has been found in anorectics with significant weight loss, but not in those who are not severely underweight.[104] When injected into the hypothalamus of rats, β-endorphin and β-enkephalin stimulated food intake, while naloxone reduced intake in obese rats and mice.[103,105] It remains unclear whether the observed association between decreased weight and increased CSF opioid activity is a compensatory response to weight loss or involved in the etiology of anorexia nervosa.[106]

Recent observations have provided morphologic evidence for the functional link between gonadal steroids and the catecholamine system. Target sites for estradiol and dihydrotestosterone have been demonstrated in the nuclei of many of the catecholamine cell bodies in the brainstem,[197] and catecholamine nerve terminals have been located in target tissues for steroid hormones.[107] Enzyme systems, particularly those responsible for the production of catecholestrogens, have been demonstrated[108] and appear to buffer the effects of estrogens in the hypothalamic-pituitary system.[67] Consequently, concentrations of catecholestrogens are much higher in the hypothalamus and pituitary. Catecholamine action then may be prolonged by the metabolic inhibition of 2-hydroxyestrogens.[68] Other enzyme systems involved in catecholamine synthesis have been studied, particularly tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. The injection of estrogens increases tyrosine hydroxylase activity, whereas progesterone causes an inhibitory effect.[109] Relating these findings to observations of anorectics provides room for speculation. With diminishing estrogen levels as a result of decreased gonadotropin, peripheral conversion of estrogen is channeled along the 2-hydroxylation pathway with a resulting increase in catecholestrogens. These agents may, in turn, inhibit the metabolism of catecholamines, which may either elevate their levels or at least potentiate their action. Pharmacologic agents such as dopamine that increase catecholamines have resulted in clinical states similar to anorexia nervosa and in lower LH levels. Decreasing the effects of catecholamines by either blocking their action or their synthesis may prove an effective treatment. Moreover, progesterone, with its inhibitory effects on tyrosine hydroxylase activity, may result in lower catecholamine levels.

Psychologic Manifestations

A variety of altered behavioral patterns are seen in those with anorexia nervosa and remains the most striking feature of this disorder. Anorectics have a perceptual distortion of body image, perceiving themselves as too fat.[16] The degree of misperception can actually be quantitated by using two moveable lights that can be manipulated until they approximate what the patient perceives as her body dimensions.[9] Experiments have revealed that anorectics consistently overestimate body dimensions to a degree consistent with the extent of malnutrition.[110] In addition, carbohydrates may aggravate these abnormalities, whereas weight gain restores normal perception.[9]

Other unusual behavioral patterns include a preoccupation with food and hyperactivity.[9] Besides an almost fanatical approach to the preparation of food and to its caloric content, anorectics have an aversion to carbohydrates, preferring fluids or protein-rich foods.[3] Periods of gorging often alternate with starvation and food avoidance,[9] although many experts classify bulima itself as a separate disorder. Altered food intake and hyperactivity have led many investigators to believe that anorectics have an abnormality in the ventromedial nucleus of the hypothalamus. Lesions in rat hypothalamus have produced similar abnormalities.[9]

Computed tomography also has demonstrated structural abnormalities in anorectics.

Cerebral atrophy and enlargement of subarachnoid space and cortical sulci have been demonstrated,[111] but the etiology and implication of this finding has yet to be discovered. The restoration of weight has reversed the atrophy in one study.[112]

Anorexia nervosa continues to be a perplexing illness, and despite endocrine abnormalities, both diagnosis and pathogenesis are most likely psychogenic. All psychologic illnesses are thought to be the result of a failure to adequately interact with the external world.[113] Anorexia nervosa can be understood as such a process, with characteristic factors that predispose, precipitate, and finally, sustain the illness.[16]

Predisposition

Little is known about what makes a person vulnerable to anorexia nervosa. Some suggest predisposing factors such as personality, family, and cultural influences.[16]

The core predisposition to the development of anorexia lies in the anorectic's difficulties in functioning autonomously and in her lack of identity. Thus, she is impaired from functioning separately from her family or other security base.[16] The origin of this fundamental problem has varied clinical interpretations. Some think that it stems from basic ego deficits in the mastery over one's own body, a "personal ineffectiveness" as a result of early interactions with parents.[114] This deficit leaves the person psychologically ill-prepared for the emotional and physical changes of normal adolescence.[115] Many of the symptoms represent a way to avoid adolescent concerns and responsibilities.[115,116] The emphasis on dieting and "weight phobia" causes the anorectic to regress to a prepubertal state in an effort to reject the new adult sexual role.[116] The characteristic age and sex distribution of anorexia nervosa may be explained by specific societal pressures placed upon the adolescent.[116,117] At the same time the adolescent is having new sexual feelings and bodily changes, society is pressuring her to control her behavior.[117] The anorectic often has an inaccurate perception of her body, which seems to be highly correlated with the degree of pathology and the prognosis.[16] Both the body image and self-satisfaction tend to be immature and appear a reflection of low self-esteem.[16,118] Whether these disturbances in body perception and self-assuredness are predisposing factors to anorexia nervosa is hard to ascertain because it is difficult to tell whether the observed characteristics are precursors or byproducts of the disease.[16] Although the personality types of anorectics vary greatly, certain characteristics are prevalent. The person often is compliant, dependent, and a perfectionist who is very directed toward goals and has high personal expectations and a need to please others.[114,116] This emphasis on conformity, and the need for the assistance and approval of others, is an external attempt to gain self-worth.[116] Early cerebral damage or a premorbid obesity have been suggested as predisposing factors and may yet prove to be contributing factors.[119] Interestingly, Turner's syndrome[120,121] and congenital urogenital malformation[122] seem to occur with increased frequency in those with anorexia nervosa. The relationship is not well defined, but perhaps the immature adolescent changes in anorectics accentuate difficulties in normal autonomy and adjustment.[16,21]

Familial predisposing factors also have been found in anorexia. A parental history of affective disorders and possibly alcoholism have been implicated,[16,123] as has a history of anorexia nervosa in siblings.[15,16] Twin studies have suggested a possible genetic influence.[124] Other investigators have found that children of obese mothers may be at risk, particularly for the bulimic group of anorectics.[125] Anorectics often come from families with high socioeconomic status, with the father working in a professional capacity.[3,126] A competitive or achievement-oriented parent may implant these values and pressures on other family members. Poor parent-child relationships and diminished communication within the family also are seen in anorectics.[3]

Sociocultural influences have been suggested as factors that predispose a person to anorexia nervosa. Leanness has become fashionable in western society,[9,127] the ideal figure today represented by actresses and models who appear "like prepubertal girls onto whom secondary sexual characteristics of mature females have been grafted."[127] An obese person is seen as less healthy, less appealing, and often slothful. Moreover, women today are under increased pressure to

be competitive and successful. These performance expectations, combined with the pressure and desire to be thin, help perpetuate the idea that weight control is self-control, which in turn implies success and achievement.[16,126] These changing social values and pressures may explain the increasing incidence of anorexia.[2,126]

Initiating Events

For many patients a precipitating event or series of events can trigger the onset of anorexia. However, the factors are varied and by no means unique to anorexia.[12,15,16] What is a common thread, though, is that the event represents a threat of loss of self-control and/or a threat to self-worth.[16] The initiating event often coincides with leaving for college or summer camp, or a parental breakup.[12,15,16,128] Sometimes a new intimate relationship may be a cause. Such events may require new demands and higher expectations, which may threaten the person's ability to control her world and body, thereby damaging her self-esteem.[12,16,128] The anorectic seeks to gain body control and feel better about herself by losing weight.[16]

Sustaining Factors

Once the disorder is clinically evident, many factors perpetuate the illness.[16] The preoccupation with food is intensified once the anorectic loses an extreme amount of weight.[16] Perceptual abnormalities of image and impaired concentration are aggravated by occasional increased carbohydrate intake,[9,16] which further intensifies the person's fear of losing control over her body. Starvation also brings about social isolation and reduced interest in the world.[16] Feeling bloated or stuffed after having eaten only small amounts is common[129,130] due to decreased gastric-emptying time.[131] This altered satiety further entrenches the aversion to food and the substitution of low calorie foods or fluids. The anorectic avoids parties and dinners because of this dread of food. The result is further social isolation.[16]

It is apparent that circumstances leading to the development of anorexia nervosa are variable and complex.[16] Furthermore, the presence of the more common predisposing characteristics do not guarantee that anorexia will develop.[16] However, once formed and triggered, the effects of weight loss and starvation lead to relentless perpetuation of the disorder.

Differential Diagnosis

Diagnosing anorexia nervosa can be difficult, and it is primarily a diagnosis of exclusion. No laboratory findings or clinical testing is unique to this disorder. Yet an early diagnosis is important to the outcome of this disease. Physician and parental sensitivity are really the only means to early recognition. The characteristic criteria for the diagnosis of anorexia nervosa are presented in Table 15-3. Since the first sign of the disorder may be amenorrhea, a systematic approach to this abnormality should be initiated. First, information re-

Table 15-3. Diagnostic Criteria for Anorexia Nervosa.

1. Age of onset prior to 25.
2. Anorexia with accompanying weight loss of at least 25% of original body weight.
3. A distorted, implacable attitude toward eating, food, or weight that overrides hunger, admonitions, reassurance, and threats.
   a. Denial of illness with failure to recognize nutritional needs.
   b. Apparent enjoyment in losing weight with overt manifestation that food refusal is a pleasurable indulgence.
   c. A desired body image of extreme thinness, with overt evidence that it is rewarding to the patient to achieve and maintain this state.
   d. Unusual hoarding or handling of food.
4. No known medical illness that could account for the anorexia and weight loss.
5. No other known psychiatric disorder, with particular reference to primary affective disorders, schizophrenia, obsessive-compulsive neurosis, and phobia neurosis. The assumption is made that even though the behavior may appear phobic or obsessional, food refusal alone is not sufficient for a diagnosis of obsessive-compulsive or phobic disease.
6. Presence of at least two of the following manifestations:
   a. Amenorrhea.
   b. Lanugo.
   c. Bradycardia (persistent resting pulse of 60 or less).
   d. Periods of overactivity.
   e. Episodes of bulimia.
   f. Vomiting, which may be self-induced.

garding previous menstrual history, the milestones of pubertal development, excessive hair growth, the possibility of pregnancy, drug ingestion, adrenal and thyroid disorders, systemic diseases, and central nervous system symptoms should be obtained. The clinician should perform a physical examination with attention to the presence of normal müllerian structures. Patients whose amenorrhea has obvious causes such as pregnancy, hyperprolactinemia, or adrenal or thyroid disorders should be separated from other amenorrheic patients. The remaining group should be evaluated systematically to determine the cause of amenorrhea.

The next step of the evaluation is the progesterone withdrawal test. If withdrawal bleeding occurs following progesterone administration, the uterus, ovaries, pituitary, and hypothalamus essentially are normal, and the patient is anovulatory. These patients would require either ovulation induction if fertility is desired or cyclic progestin administration to protect the endometrium from continuous estrogen effect. If withdrawal bleeding does not occur, the defect is uterine in origin or the patient does not have endogenous estrogen stimulation of the endometrium. Those with anorexia often fall into the latter category, but some anorectics are anovulatory and do respond to progesterone withdrawal. Patients who fail to bleed after progesterone administration should then be treated with estrogen for 1 month, after which the progesterone withdrawal test is repeated. Failure to respond by bleeding suggests that the uterus is incapable of responding to hormones. If withdrawal bleeding occurs, the uterus is normal but has not been stimulated by ovarian hormones.

Ovarian evaluation proceeds with the measurement of gonadotropin concentrations. An elevated FSH concentration (usually greater than 50 mIU/ml) is characteristic of ovarian failure because the ovarian hormone secretion is inadequate to lower gonadotropin levels. Patients whose amenorrhea is caused by anorexia nervosa have normal or low-normal gonadotropin concentrations, indicating that the anterior hypophysis is not being adequately stimulated to secrete gonadotropin concentrations capable of stimulating ovarian function. In such cases, the cause of amenorrhea is presumed to be at the level of the hypothalamus. In the absence of neurologic localizing signs, the most common causes of hypothalamic amenorrhea are nutritional, stress-related, exercise-related, or a combination. Pituitary provocative studies may be done to ensure the normal stimulation and secretion of other pituitary hormones. Even in the absence of demonstrable pathology, these patients should be evaluated periodically to exclude a slow-growing tumor or other disorder.

In addition to amenorrhea, weight loss is often the presenting complaint. The clinician should take a history that includes information on the ingestion of drugs that may cause nausea and vomiting, and laxative abuse. Further history and physical examination must distinguish anorexia nervosa from such disorders as infections (e.g., tuberculosis); collagen vascular disorder; adrenal or thyroid disorder; blood dyscrasias such as leukemia; anemia or cardiac abnormalities; renal or liver disease; malabsorption states (i.e., ulcerative colitis, Crohn's disease, pancreatic insufficiency); and neoplasias of the stomach, colon, pancreas, or other organs. The possibility of psychologic disturbances also should be investigated. A variety of depressive disorders, bulimia without anorexia, schizophrenia with bizarre eating patterns, and Kleine-Levin and Kalver Buchy syndromes can mimic the disorder.[132] In any young patient who loses weight and has amenorrhea, the diagnosis of anorexia nervosa should be strongly considered and the patient questioned about her body perception and eating behavior. Claims of "feeling fat" when there is obvious weight loss, intense fears of obesity, and a history of unusual eating behavior all aid in the diagnosis of anorexia nervosa.

Treatment

Management of this disorder is widely debated.[9] Treatment has included combinations of drugs with various psychotherapy techniques. Increasingly, authors emphasize early recognition of the disease so that treatment can be started prior to full development of the syndrome.[9] The major goal of all therapy is weight restoration. Any successful program

incorporates efforts by the primary physician, a psychiatrist, and a nutritionist. To alleviate her fears of excessive weight gain, the patient should be reassured that the target weight gain is within the normal range. Beyond that, improving self-esteem, independence, and communication between family members is encouraged.[133]

Drug therapy was initially received with great enthusiasm as more investigators became aware of the various neurotransmitter abnormalities in anorexia. Despite initial enthusiasm, however, more work is needed. Cyproheptadine, a serotonin antagonist, has been useful in nonanorectics but has not been effective in anorectics.[133] Lithium may be helpful for the often hyperkinetic state but probably should be avoided because of possible electrolyte imbalances.[134] Anabolic steroids can cause virilization.[3] Tricyclic antidepressants have been used in those patients who have depressive symptoms following adequate weight restoration.[133] Adrenergic blockers block the norepinephrine activity thought to be elevated in anorectics.[97] Chlorpromazine may be helpful with a behavior modification program because its sedative effects may allow for more effectiveness.[133] Some treatment programs also have used L-dopa but with varying results.[101] Recent observations of elevation of catecholestrogens and increased tyrosine hydroxylase activity with increased catecholamine synthesis and potentiation may lead to therapies designed to decrease catecholamine activity. Progesterone's inhibitory activity on tyrosine hydroxylase may be beneficial, possibly in combination with estrogen. Estrogen-progestin replacement is advocated to prevent long-term effects of estrogen depletion such as osteoporosis. In those who remain anovulatory, a cyclic progestational agent should be given. Withdrawal bleeding implies an endogenous estrogen effect on the uterus, which could cause endometrial hyperplasia. Patients who want to become pregnant should be reassured that normal ovulation should return with weight gain.[3,16] Ovulation induction with clomiphene citrate or human menopausal gonadotropin (HMG) and human chorionic gonadotropin (HCG) may be necessary. No adverse effects on antepartum course, labor and delivery, or postpartum course are known to result from this therapy.[13,35]

Behavioral therapy is considered superior to drug therapy in the restoration of weight.[133,135] Initial management for severe cases has included intravenous fluids and nasogastric feedings.[9] Hyperalimentation also has been advocated.[136] Individual and family psychotherapy is needed to correct the psychopathology associated with anorexia. Behavior modification to change eating habits is often required. The patient is admitted to the hospital and a target weight is determined, with discharge contingent upon meeting and maintaining that weight.[137] Thereafter, rewards are given for incremental weight gain; otherwise, the patient is isolated. The patient and her family continue therapy, which emphasizes emotional growth, the improvement of self-esteem and expectations, and open communication between family members.[138,139]

A good prognosis can be achieved in 70% of anorectics.[9] Poor prognosis is associated with extreme weight loss, older age of onset, longer length of illness, and bulimia.[3,140] In addition, lower socioeconomic status and poor social adjustment and parental relationships are associated with guarded prognosis.[3,140] Males appear less likely to recover than females.[3,9,140] Mortality rates vary from 2 to 10%.[9] Death often occurs from cardiac arrhythmias secondary to electrolyte imbalances, although deaths from unrecognized infections, lowered basal temperatures, thermal regulation difficulties, gastric dilatation and perforation, and aspiration have been reported.[13]

Weight restoration corrects all of the metabolic abnormalities in the absence of clinical symptoms. Amenorrhea may persist in as many as 50% of patients, while perceptual abnormalities and preoccupation with food also may continue in some cases.[9]

Stress-Related Amenorrhea

It has long been known that menstrual function may be influenced by stress. Ten to 19% of women entering religious life have secondary amenorrhea.[23] Twenty-five percent of women entering the British army[141] and 50% of young girls committed to institutions had loss of

menses.[142] Similar observations have been made in women in concentration camps,[21] nursing schools,[22] and colleges.[143] All had secondary amenorrhea prior to any alteration of diet, sleep, or activity, which implies that the loss of menses was related to stress. Interestingly, although the environment remained unchanged, menstrual function returned in many within 103 days. It is possible that these women had simply adjusted to events, thereby reducing stress levels. This finding illustrates that exposure to an unfamiliar environment is one of the primary reasons for stress. As the person is repeatedly exposed, her initial endocrine responses become blunted or extinguished as she adapts. These responses are highly individualized and reflect interaction between a person and her environment.[144] Although a variety of endocrinologic responses have been studied in response to stress, the exact mechanisms that trigger menstrual disturbances are still unknown. With known interaction between emotional, hypothalamic, and pituitary function, we can surmise that stress-related endocrinologic changes could influence menstrual function.

Table 15-4. Summary of Endocrinologic Changes.

CBC
WBC ↓
Lymphocytes ↑
BUN ↑
Glucose ↓
Insulin ↑ or ↓
Total T3 ↓
Total T4 ↓
Reverse T3 ↑
TSH →
Cortisol ↑ (flat or reversal diurnal variation)
Estrogen → or ↓
(EFP)
Serum lipids ↑ or ↓
17-OH ↓
17-KS ↓
GH ↑
PRL →
ADH ↓
Serotonin ↑
Catecholestrogens ↑
(2-OH E_2)
Potassium (serum) ↓
Serum carotene ↑
Albumin →

Endocrine Abnormalities

Catecholamines

Epinephrine and norepinephrine synthesis and release are sensitive to a wide variety of stimuli.[145] Their effects on body regulation are multiple but particularly important in regulating blood distribution via blood pressure and heart rate, and the distribution of blood to critically dependent areas. Multiple studies have shown that norepinephrine and epinephrine increase during stress.[146,147] Rises in epinephrine also occurred in novel and unpredictable situations.[146] Epinephrine levels fell once the person became adjusted to or mastered the situation.[146] Norepinephrine levels were elevated during stress, but the rise was related more to the amount of vigilance or attention needed for the situation.[146] Furthermore, catecholamine responses do not extinguish as rapidly as cortisol concentrations when reexposed to stimuli.[148–150] Other studies have found that tyrosine hydroxylase and phenylethyamine-*n*-methyl-transferase, enzymes involved in catecholamine synthesis, were significantly increased in stressed animals.[150] Thus, both the concentrations of catecholamines and the capacity for catecholamine synthesis increase with stressful stimuli. These findings can possibly influence menstrual function. Catecholamine action may result in the redistribution of blood flow from the ovaries or even the pituitary, which in turn influences hormone synthesis and secretion. Similarly, catecholamine action on both the hypothalamus and pituitary directly may result in lowered gonadotropin secretion.

Other catecholamines, specifically dopamine, affect the regulation of gonadotropin production but have not been studied extensively in response to stressful stimuli. However, with norepinephrine elevation during stress, dopamine concentrations also may be altered. Indirect evidence for altered dopamine levels may be gathered from known observations of prolactin responses. Serum prolactin concentrations are elevated in response to stressful stimuli.[151,152] During surgery[152] and even during pelvic examinations,[153] prolactin levels increase. Relation-

Table 15-5. Summary of Dynamic Testing with Anorexia Nervosa.

TRH
Delayed but normal TSH ↑
Normal PRL ↑
LHRH
↓ LH response
↑ FSH response
Clomiphene citrate stimulation
↓ LH response
ACTH → or ↑ response
GTT abnormal
Insulin tolerance test
→ GH response
EKG
Low voltage
Inverted T wave

ships to psychologic stimuli are less studied, however.[144] Stimuli must be intense and constant to evoke a response,[144] although increases are found even prior to gynecologic examinations. Elevated dopamine levels act as a prolactin inhibitory factor, lowering prolactin levels.[154] A lack of dopamine would result in elevated prolactin levels. Elevated concentration influences menstrual function both at a central level by influencing gonadotropin release and synthesis and by blocking their action on the ovaries' steroid production. Prolactin also may enhance androgen production by the adrenal gland.[155]

Cortisol

Cortisol secretion in response to stress has been studied extensively. Soldiers, parachute jumpers, prisoners, and marathon runners have elevated cortisol secretion.[149,156–158] Cortisol secretion also is elevated prior to surgery,[159] in crying infants,[160] and in the parents of children dying of leukemia.[161,162] Cortisol secretion is increased in novel or unfamiliar situations, but upon reexposure to the stimuli significant elevations do not occur.[144,163,164] Similar observations have been made regarding ACTH production.[164] Increased levels to initially stressful stimuli decrease with repeated exposure. Other studies have shown in response to stress that hypothalamic and pituitary cells increase production of a large molecule called "big ACTH."[165] Under stress this molecule is broken down into fragments of ACTH and *b*-lipotropin. *b*-Lipotropins, in turn, can be metabolized to endorphins and enkephalins.[165] Under these circumstances, preferential synthesis occurs so that ACTH is the major product of the pituitary, while hypothalamic secretion of endorphins is increased.[166] Neural cells involved in secretion of endorphins have been found in close proximity to nerve cells involved in dopamine neurotransmission and GnRH production.[166,167] Endorphins decrease gonadotropin release, possibly by influencing hypothalamic GnRH release or pulsatile nature.[167] The elevated ACTH—the other fragment of "big ACTH"—may result in elevated cortisol secretion by the adrenal gland until negative feedback diminishes ACTH production. In this fashion, elevated cortisol seen in response to stressful stimuli may be the result of endorphin elevation and increased cortisol secretion. Some studies, however, have demonstrated that cortisol suppresses LH secretion by the pituitary and LH-induced steroidogenesis in the testes.[168] Perhaps cortisol also affects ovarian steroidogenesis, thus interfering with menstrual function.

Other hormones studied in response to stress have included growth hormone and testosterone. Increases of growth hormone during stress have paralleled that of cortisol and catecholamines.[144] Elevated levels have been seen following surgery,[169] written and oral examinations,[170] psychologic testing,[171] and exercise.[172] These responses appear to require a higher threshold of stimulus intensity before levels increase.[173] Growth hormone secretion is influenced by both a hypothalamic releasing factor and an inhibitory factor called somatostatin. The regulation of these substances is complex and influenced by different neurotransmitters, levels of glucose, and amino acids. Growth hormone and its elevation during stress probably has little direct influence on menstrual dysfunction. Decreased levels of testosterone occur following exposure to a wide variety of stressful stimuli.[174,175] The mechanism remains unclear but seems unrelated to LH or FSH levels.[176] This decrease may be secondary to elevated glucocorticoids, either by suppressing LH production or by interfering with steroidogenesis in the gonad.[168] No prospective studies

of estrogen and progesterone in response to stressful stimuli have been done.

Much is unknown about stress and its relationship to menstrual dysfunction. Although a long-recognized phenomenon, the exact mechanism by which stress affects menses is unknown. At present, the most encouraging finding appears to be the observance of "big ACTH" with its ultimate effects on neuropeptides, particularly endorphins. Diagnosis, however, should remain a process of exclusion. Other causes of amenorrhea—physical, drugs, metabolic, endocrinologic—should be investigated and corrected. If other possibilities have been exhausted and the woman is under stress, attributing the amenorrhea to stress may be justified. Treatment begins with eliminating or at least minimizing the stress. This may include psychotherapy. Regular menstrual function and subsequent ovulation should return when the stress is eliminated. In patients whose amenorrhea persists, ovulation induction may be necessary.

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Adolescent Nutrition 16

Starr Gantz

Adolescence is unique in the growth and development process. Adequate nutrient intake and stores during childhood enhance the onset of puberty; thus, tall, heavier children enter puberty earlier than those who are shorter and weigh less.[1] The habits and patterns developed during childhood may be tossed aside as the adolescent becomes independent, tests adult roles, and seeks social acceptance. Equally important is the ability to define and cope with a changing body and self-image. Optimum nutrition during adolescence is necessary if the demands of growth are to be met. These demands include increases in height and weight, deposition and redistribution of fat, increased lean body mass and the enlargement of organs including those which enable the adolescent to become sexually mature and fertile.[2]

Common nutritional disorders which affect adolescents include obesity, anorexia nervosa (Chapter 15), and anemia (Chapter 19). An adolescent unable to cope with the many changes occurring in her body may use food as a defense, thereby compromising optimal growth.

Nutrient Requirements

Several factors must be considered in determining the nutrient and energy needs of the adolescent. These include (1) physical activity, (2) body size and composition, (3) age, (4) climate and ecologic factors, and most important, (5) the velocity of the growth curve.[3] The psychologic and cognitive changes occurring during adolescence can also affect nutrition.

The linear spurt in adolescence provides about 15% of the final adult height, while the weight spurt accounts for approximately 50% of the young adult's body mass. It is understandable that peak requirements coincide with maximum growth.[3] The series of events during pubescence and the growth spurt are predictable.[4] However, the onset of maturation and the growth spurt is unique in every case. Ideally, nutritional requirements should be correlated to the biologic age or stage of sexual maturity rather than to chronologic age.[5]

Heald and Jacobson identify three specific traits of adolescence that directly affect nutritional requirements.[3] First, the body mass almost doubles during the growth spurt. Secondly, energy and protein requirements, which are linked to the growth spurt, are higher than at almost any other time of life. Finally, the adolescent is highly sensitive to energy restriction because of the increasing anabolic need.

Only limited research has been done to determine nutritional requirements for the adolescent. The requirement levels are the result of a few animal experiments and/or have been interpolated from adult maintenance figures with an additional amount for growth.[6] The current Recommended Daily Allowances (RDA), published by the Food and Nutrition Board of the National Research Council in 1980, take into account the known or estimated variability in requirements,

Table 16-1. Recommended Daily Dietary Allowances,[a] Revised 1980.

	Age (years)	Weight (kg)	Weight (lb)	Height (cm)	Height (in)	Protein (g)	Fat-Soluble Vitamins: Vitamin A (μg)[c]	Vitamin D (μg)[c]	Vitamin E (mg α-TE)[d]
Females	11–14	46	101	157	62	46	800	10	8
	15–18	55	120	163	64	46	800	10	8

	Water-Soluble Vitamins: Vitamin C (mg)	Thiamine (mg)	Riboflavin (mg)	Niacin (mg NE)[3]	Vitamin B_6 (mg)	Folacin (μg)[f]	Vitamin B_{12} (μg)
Females	50	1.1	1.3	15	1.8	400	3.0
	60	1.1	1.3	14	2.0	400	3.0

	Minerals: Calcium (mg)	Phosphorus (mg)	Magnesium (mg)	Iron (mg)	Zinc (mg)	Iodine (μg)
Females	1200	1200	300	18	15	150
	1200	1200	300	18	15	150

[a]The allowances are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods in order to provide other nutrients for which human requirements have been less well defined.
[b]Retinol equivalents. 1 retinol equivalent = 1 μg retinol or 6 μg β-carotene.
[c]As cholecalciferol. 10 μg cholecalciferol = 400 IU of vitamin D.
[d]α-Tocopherol equivalents. 1 mg D-α-tocopherol = 1 α-TE.
[e]1 NE (niacin equivalent) is equal to 1 mg of niacin or 60 mg of dietary tryptophan.
[f]The folacin allowances refer to dietary sources as determined by *Lactobacillus casei* assay after treatment with enzymes (conjugases) to make polyglutamyl forms of the vitamin available in the test organism.
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thereby providing a margin of safety. The factors that influence the efficiency of nutrient utilization also are taken into consideration.[3] Because of technical difficulties, however, these are listed according to chronologic rather than gynecologic age.

Normal Nutrient Needs

Energy

Currently, the RDA is the best evaluation tool available for nutrient needs. However, to ensure accuracy each adolescent's needs should be individually determined (Table 16-1).

The energy RDA for the adolescent female includes different ranges of kilocalories for each age group to compensate for the varying growth rates. The recommended energy allowance for the 11- to 14-year-old is 1500-3000 kcal, and 1200-3000 kcal for girls 15 to 18.

Wait et al investigated the relationship of age, height, weight, size, and surface area to the energy needs of healthy, well-nourished children.[7] They found that the rate of energy intake increased as the rate of growth increased. In their study, children's energy intake for each unit of weight decreased with age, while intake per unit of height increased. The use of surface area resulted in a constant energy intake during puberty. When age was included, the relationship between body size and energy intake stabilized. Their concluding data showed that relating age and total energy to height or energy for each unit of height are effective methods to determine energy needs.

Heald et al reported on the caloric intake of 2750 girls from 11 states who represented diverse socioeconomic conditions, cultural and ethnic origins, and geographic distribution.[8] They found that the average daily intake for 6-year-olds was 1670 calories and rose steadily to 2250 calories at age 12. The intake gradually decreased to 2200 calories at age 18. Thus, the peak caloric intake coincided with the peak in growth spurt. The decrease in caloric intake after age 12 may be due to decreased demand for the nutrients essential to growth. Data from the Ten-State Nutrition Survey concurred with these findings.[9]

Protein

Surveys reveal that protein supplies 12–14% of the energy intake of adolescents.[8,10] The peak protein intake occurs at 12, the same age as the peak caloric intake. In the survey, girls ate approximately 80 g of protein per day, well above the RDA. This leads to the question of whether Americans eat too much protein. The FAO/WHO Expert Committee recommends a progressive decrease of protein intake from childhood to adulthood.[11] Intake would continue to increase with growth, but the amount per kilogram would decrease with age. Adolescents who have limited food intake because of dieting or economic factors compromise their energy intake and protein utilization. When energy intake is insufficient, dietary protein is drawn upon to meet energy demands and is not available for the synthesis of new tissue. The result is a reduction in the growth rate, despite what appears to be normal protein intake.

Minerals

Calcium

The skeleton represents about 99% of the body's total calcium. The dietary needs, therefore, are related to the formation and maintenance of bone. The tremendous increase in skeletal length and mass during adolescence has a significant impact on dietary requirements. Two factors have made it difficult to establish requirements for any age group. First, equilibrium can be achieved on a wide range of intakes. Secondly, mistakes in measuring intakes and/or excretion can cause errors in calculating calcium balance.[3]

Retention of calcium will vary with the growth rate, but girls at their peak will accumulate 210–240 mg per day.[12] The RDA is set at 1200 mg per day to meet the needs of the fastest growing adolescent. Since it is very difficult to meet this level without including milk products, the dieting adolescent female who eliminates milk products from her diet is at risk of limited calcium intake. One survey of adolescent girls revealed that 50% consumed less than two-thirds of the RDA.[13] Either an excess intake of phosphorus from soft drinks and foods containing phosphorous additives or a reduced calcium intake may compromise optimal calcium status. However, this is controversial.[14]

Iron

Various surveys have shown that the adolescent diet is iron deficient. In one survey of adolescents from diverse socioeconomic backgrounds, 5 to 15% had below normal hemoglobins or hematocrits.[15,16] Black children also had a higher incidence of anemia.[16] Factors such as genetics, hormones, and diet complicate the interpretation of the role of iron in these data.[17]

The primary role of iron is the expansion of blood volume and muscle mass during growth. Girls require 32 mg of iron per kilogram of weight gain.[18] Additional iron lost from menstruation averages about 0.5 mg per day.[19] This brings the RDA to 18 mg per day.

Expecting an adolescent to consume 18 mg of iron each day is unrealistic. Surveys show that girls between 12 and 16 consume about 9 to 13 mg per day, hence the high incidence of anemia and the need for supplementation.[19] The adolescent should be encouraged to eat good sources of iron (red meats, dried beans, iron-fortified cereals) every day. The combination of ascorbic acid and nonheme iron sources improves the absorption of iron from these foods.[17] Adolescents with good iron stores absorb less than those who are iron deficient.

Zinc

The zinc requirement for children entering adolescence is greater because of their acceler-

ated growth.[20] The RDA is set at 15 mg per day. A survey of adolescent girls revealed that more than one-third consumed less than two-thirds of the recommended daily intake.[21] This is a health risk.

The best sources of zinc are meat, poultry, and seafood. A correlation between zinc and protein has been found in diets containing both animal and vegetable protein sources. For every 10 g of protein, 1.5 g of zinc also was present. This drops when vegetable proteins replace animal sources.[22]

Vitamins

Vitamin requirements for the adolescent have not been established because of insufficient data. They are interpolated based on adult and infant requirements. The requirements are set at a level to prevent symptoms of deficiency and/or alterations in biochemical or physiologic functions.[3] The need for vitamins increases during adolescence because of the greater demands of growth.[23] The RDA for vitamins are listed in Table 16-1. The essential functions, deficiency states, and current survey data for the fat- and water-soluble vitamins are provided in Tables 16-2 and 16-3.

The Pregnant Adolescent

Adolescent pregnancy poses unique physiologic and social problems that alter the usual nutritional requirements of pregnancy. Pregnancy outcome in the teenager is influenced by a composite of factors—psychosocial and cultural, medical and health, dietary and metabolic. The clinician must take them all into account.

The pregnant teen's environment is extremely important. Factors such as home, income, marital status, employment, school attendance, and family support influence her nutritional status and future intake. Even more important are her feelings about the pregnancy, the baby, and herself.

The following statistics show the importance of maternal good health and prenatal care: the maternal death rate is 60% higher for the teen under 15, and 5% higher for the 15–19 age group. The lack of prenatal care in the first

Table 16-2. Summary of Fat-Soluble Vitamins.

	A	D	E	K
Active compounds	Retinol (A_1) 3-Dehydroretinol (A_2) Retinal Retinoic acid Carotenoids	Cholecalciferol (D_3) Ergocalciferol (D_2) 25-OH-D 1,25-$(OH)_2$D	Tocopherols (e.g., α, β, δ) Tocotrienols	Phylloquinone (K_1) Menaquinone (K_2) Menadione
Essential function	Maintains function of epithelial cells, mucous membranes, skin, bone; constituent of visual pigments	Calcium and phosphorus absorption and utilization in bone growth[3]	Protects cell structures	Necessary in formation of four factors essential for clotting of blood
Deficiency: signs and symptoms	Night blindness; glare blindness; rough, dry skin; dry mucous membranes; xerophthalmia	Rickets; soft bones; bowed legs; poor teeth; skeletal deformities	Increased hemolysis of red cells; creatinuria; anemia, edema, and skin lesions in infants	Low concentration of clotting factors; increased clotting time; hemorrhagic disease of newborn
Reported findings	The Ten-State Nutrition Survey revealed that 40% of Spanish-American teens and approximately 10% of black and white teens had low plasma levels of vitamin A.[24]			

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Table 16-3. Water-Soluble Vitamins.

	Ascorbic Acid	Thiamine	Riboflavin	Niacin
Essential function	Formation of collagen; cellular oxidation and reduction	Energy metabolism; coenzyme forms TPP (cocarboxylase)	Carbohydrate, fat, and protein metabolism; coenzyme forms FMN and FAD	Carbohydrate, fat, and protein metabolism; coenzyme forms NAD and NADP
Deficiency: signs and symptoms	Scurvy; sore mouth; sore and bleeding gums; weak-walled capillaries	Beriberi; poor appetite; fatigue; constipation	Eye sensitivity; cheilosis (humans)	Pellagra; dermatitis; nervous depression; diarrhea
Reported findings	Low intakes of vitamin C with no clinical manifestations have been reported, suggesting that even less than optimal levels can maintain vitamin C status[17,25]			

trimester is responsible for the high death rate. (Twenty percent wait until the third trimester to seek care.[28])

The American Academy of Pediatrics identifies low-birth-weight infants and preeclampsia as the two major complications of teenage pregnancy.[29] The incidence of babies weighing less than 2500 g is higher in adolescents than in older women.[30] Moreover, an adolescent, regardless of her chronologic age, is more apt to give birth to a low-weight infant if she has a low gynecologic age.[31]

The maternal nutritional status also influences the pregnancy outcome. Studies have shown that inadequate intake of calories, iron, calcium, and vitamin A can compromise adolescent growth and the pregnancy.[32,33]

The American College of Obstetricians and Gynecologists has identified 12 nutritional risk factors that are closely correlated to the nutritional problems frequently seen in the pregnant adolescent.[34] The obstetric patient is at risk if at the onset of pregnancy:

1. She is an adolescent (15 or younger). Those who are under 15 are at risk because the demands of pregnancy burden the still growing body.
2. She has had three or more pregnancies within 2 years. This young woman is more likely to have depleted nutrient stores, which can compromise maternal and fetal outcome.
3. She has a history of reproductive problems. Previous abortions, pregnancy complications, low-birth-weight infants, or perinatal loss signal that the current pregnancy is at high risk.
4. She is economically deprived. This patient should be referred to assistance programs.
5. She is a food faddist. If the girl has unusual food habits, she is probably not getting an adequate supply of nutrients.
6. She is a heavy smoker, drug addict, or alcoholic. The patient who smokes more than 20 cigarettes a day, the drug addict, and the alcoholic who drinks 5 ounces of hard liquor daily are risking major physiologic and nutritional problems. The lifestyle which accompanies drug addiction or alcoholism usually includes an inadequate diet, along with an altered metabolism.
7. She has a chronic systemic disease. Problems such as anemia, thyroid dysfunction, and gastrointestinal disorders may interfere with ingestion, absorption, or the utilization of nutrients. The drugs used for treating these conditions also may affect nutritional status.
8. She does not have a good prepregnant weight. The patient is at risk if her weight is below 85% or above 126% of the standard

Vitamin B_6	Folacin	Vitamin B_{12}	Pantothenic Acid	Biotin
Metabolism of amino acids; coenzyme forms PALP	Growth; blood formation; synthesis of DNA, RNA, choline; amino acid interconversions;	Blood formation; choline synthesis; amino acid metabolism; maintenance of nervous system	Carbohydrate, fat, and protein metabolism; constituent of co-enzyme A and acyl carrier protein	Carboxylation reactions; fatty acid synthesis; gluconeogenesis; amino acid catabolism
Convulsions; anemia renal calculi	Megaloblastic anemia; glossitis; diarrhea	Macrocytic anemias; sprue and pernicious anemia	General malaise; abdominal soreness and cramps; weakness and cramping of legs; tenderness in the heels; insomnia	Lassitude; anorexia; depression; anemia
In a survey of 127 female adolescents, almost half had diets containing less than 66% of the RDA.[27]	In the Daniel et al survey of girls from low-income families, 47% had below normal plasma concentrations of folacin[26]			

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for her height. A high percentage of adolescents are either underweight or obese.

The obstetric patient is likely to be at risk nutritionally if the following conditions develop:

1. Anemia. The demand for iron for both the mother and fetus during pregnancy is about 800 mg. Many pregnant adolescents have iron-deficiency anemia. Although mild nutritional anemia has little effect on the developing fetus, the mother can develop serious problems such as severe anemia, hemorrhage at delivery, atypical cytology of the cervix, thrombocytopenia, and an increased risk of transfusion.
2. Inadequate weight gain. Signs of fetal and maternal malnutrition include:
   a. Failure to gain weight (less than 2 lb per month).
   b. Actual weight loss.
   c. Significant nausea and vomiting during early pregnancy.
   d. Poor or delayed uterine fetal growth.
3. Excessive weight gain. Some adolescents are inactive during pregnancy and as a result gain too much weight. Overeating may be the teenager's way of dealing with the psychologic impact of her pregnancy.
4. Demand of lactation. The nursing mother has special dietary requirements which help her provide an additional 1000 calories per day to her baby. During pregnancy she needs to build up fat stores that help meet the needs of lactation.

Two goals have been set for the adequate nutrition of the pregnant adolescent: (1) a dietary intake as close as possible to the RDA and (2) a weight gain of at least 25 lb.[35] Studies have shown that adequate weight gain during pregnancy has a positive influence on birth weight.[36,37]

In determining the RDA for the pregnant adolescent, the adult increment for pregnancy is added. Since these do not take into account the pregnant adolescent's gynecologic age and stage of velocity of growth, the nutritional needs of each pregnant adolescent must be individually assessed. The RDA for the pregnant adolescent are listed in Table 16-4. Supplements frequently are prescribed to meet these levels.

It may be difficult to achieve the nutritional and behavioral changes necessary for a good outcome for mother and child. However, education, a supportive health team that provides medical, social, and nutritional services, and a supportive family can have a positive effect on both the pregnant adolescent and her baby.

Table 16-4. Recommended Daily Dietary Allowances, Revised 1980.

	Age (years)	Weight (kg)	Weight (lb)	Height (cm)	Height (in)	Protein (g)	Fat-Soluble Vitamins: Vitamin A (μg RE)	Fat-Soluble Vitamins: Vitamin D (μg)	Fat-Soluble Vitamins: Vitamin E (mg α-TE)
Pregnant						+50	+200	+5	+2
Lactating						+20	+400	+5	+3

	Water-Soluble Vitamins: Vitamin C (mg)	Thiamine (mg)	Riboflavin (mg)	Niacin (mg NE)	Vitamin B_6 (mg)	Folacin (μg)	Vitamin B_{12} (μg)
Pregnant	+20	+0.4	+0.3	+2	+0.6	+400	+1.0
Lactating	+40	+0.5	+0.5	+5	+0.5	+100	+1.0

	Minerals: Calcium (mg)	Phosphorus (mg)	Magnesium (mg)	Iron[a] (mg)	Zinc (mg)	Iodine (μg)
Pregnant	+400	+400	+150	—	+5	+25
Lactating	+400	+400	+150	—	+10	+50

[a]The increased requirement during pregnancy cannot be met by the iron content of habitual American diets nor by the existing iron stores of many women; therefore the use of 30–60 mg of supplemental iron is recommended. Iron needs during lactation are not substantially different from those of nonpregnant women, but continued supplementation of the mother for 2–3 months after parturition is advisable in order to replenish stores depleted by pregnancy.

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Lactation

More women are breast-feeding their babies, a method that offers definite advantages to both baby and mother. The advantages to the baby include (1) fewer infections, (2) fewer allergies, (3) better digestion and absorption, (4) safety and convenience, (5) emotional satisfaction, (6) fewer dental problems, (7) the development of strong oral muscles, and (8) the decreased chance of overfeeding.[38,39] The advantages to the mother include (1) a return to normal size through the use of body fat, (2) a delay in ovulation which delays menses but is not an effective contraceptive, (3) emotional bonding, and (4) safety and convenience.[38,39]

There are no known disadvantages to the infant who is breast-fed, but if she should fail, sometimes the nursing mother feels guilt, anxiety, shame, embarrassment, inconvenience, and the inability to make a commitment.

The University of Kentucky Medical Center's Young Parents Program has identified two disadvantages specific to the adolescent. First, she views her breasts as sexual objects rather than as food sources. And second, an adolescent who is still growing and/or whose diet history shows marginal or deficient nutrient intakes may not be able to support breast-feeding.

Determinants of Eating Patterns

With adolescence comes new experiences and changes in lifestyle. The adolescent seeks independence and spends more time away from home where she has the opportunities to make more food choices.

Schorr found that factors such as social participation, teen employment, parental occupation, and the educational level of the mother all influenced food intake. On the other hand, age, sex, family size, and nutrition information did not.[25]

Adolescents also are concerned with their body image. One study revealed that 70% of the females wanted to lose weight, yet only about 15% were actually obese. Females also want smaller hips, thighs, and waists.[40,41] Advertising and the media contribute to the adolescent's preoccupation with perfect body image by promoting a certain "look" that is difficult for most girls to achieve.

Peer pressure and the desire to be accepted probably have the strongest influence on food

choices. The adolescent, in her eagerness to be accepted, may adopt unusual eating habits such as vegetarianism, fad weight loss diets, and heavy alcohol consumption.[14] All may compromise growth.

Adolescents are notorious for being meal skippers, filling in the voids with snacks. In Huenemann's survey, whites and orientals missed fewer meals than blacks. Huenemann found that as meal regularity increased so did nutrient content and socioeconomic status. Breakfast and lunch were more often skipped than dinner.[42]

Studies have shown that snacking contributes significantly to the total daily nutrient intake.[43–45] Unfortunately, snack items usually lack calcium and iron. A 1972 survey of food preferences found that adolescents' top five choices were soda pop, milk, steak, hamburger, and pizza.[25] The adolescent who chooses snacks from vending machines, convenience stores, and snack bars is apt to be eating high calorie food with very little nutritional value.

Fast-Food Restaurants

Fast-food restaurants are attractive to the adolescent because the food is good, fast, and affordable.[46] Most fast foods are good sources of protein and B vitamins but tend to be high in calories, and low in calcium and vitamins A and C.[47] This does not mean the adolescent needs to avoid these restaurants. Before ordering, however, she needs to consider what has been eaten that day and how this fast-food meal will fit into the day's intake. The goal should be to choose an item from each of the four food groups. The National Dairy Council has developed a leaflet that lists a variety of food items from various national fast-food chains and puts them into the basic food groups (Table 16-5). It also lists the nutritional pros and cons of several menus. Table 16-6 illustrates how the adolescent can eat fast food and still not be shortchanged nutritionally.

Milk and milk products are our major source of calcium, a nutrient that is important for developing healthy bones and teeth in children and teenagers. Adults also need calcium to keep muscles functioning and to help prevent osteoporosis, a degenerative bone disease. Add a serving from the milk group to this meal by:

Choosing milk instead of a soft drink.
Choosing a milk shake, if it is made with real milk.
Choosing a cheeseburger instead of a regular hamburger, if it is made with real cheese.
Choosing the recommended servings from the milk group at other meals during the day (Table 16-3). A serving is 1 cup or milk or yogurt, or 1.5 ounces (1.5 slices) of cheese.

Weight Loss: Fad Diets

In their effort to have the "ideal" body, adolescents are susceptible to fad diets that compromise growth and health. Most of these diets promise instant weight loss with a minimum of effort. True, people often do lose weight quickly on these diets, but usually gain it back just as quickly. The body is stressed if fad dieting is done repeatedly. Because whole food groups or classes are omitted, the adolescent may be deficient in one or more nutrients.[48]

The following is a review of three of the most popular weight loss regimens:[49]

The Scarsdale Diet

This is a ketogenic diet that is low in carbohydrate, so that fat deposits are broken down for energy at a faster rate than the body can use them. The fatty acids bind together to form ketone bodies that stress the body's ability to maintain balance between acid and alkaline. The kidney must excrete the ketone bodies in the urine. The dieter starts losing large amounts of water and, in turn, a quick and substantial amount of weight. Similar diets include the Mayo Clinic Diet, Dr. Stillman's Quick Weight Loss Diet, and Dr. Atkins' Diet Revolution.

Low-Calorie Protein Diets

The dieter buys a flavored powder that can be mixed with water and drinks it three times a day instead of ingesting other food. Each serving contains 110 calories, a total of 330 per day. Although the mix has vitamins and

Table 16-5. Fast Food and the Basic Four Food Groups.

Food Group	Milk Group	Meat Group	Fruit-Vegetable Group	Grain Group	"Others" Category
Recommended daily number of servings	3 for children 4 for teenagers 2 for adults	2 for all ages	4 for all ages	4 for all ages	None
Most important nutrients	Calcium Riboflavin (B_2) Protein For strong bones and teeth, healthy skin, and good vision	Protein Niacin Iron Thiamine (B_1) For muscle, bone, and blood cells; healthy skin and nerves	Vitamin A Vitamin C To resist infections, heal wounds, and for night vision	Carbohydrate Thiamine (B_1) Iron Niacin For energy and a healthy nervous system.	Carbohydrate Fat These foods, low in most nutrients, are usually high in calories

Fast Food Item	Number of Calories	Milk Group	Meat Group	Fruit-Vegetable Group	Grain Group	"Others" Category
McDonald's Big Mac	563	Cheese	Hamburger	Onion, lettuce	Roll	Pickles, sauce
Burger King Whopper	670	—	Hamburger	Onions, lettuce, tomato	Roll	Catsup, pickles, mayonnaise
Taco Bell: beef taco	186	Cheese	Beef	Lettuce	Taco shell	—
Taco Bell: bean burrito	343	Cheese	Refried beans	Onions	Flour tortilla	Sauce
Wendy's Chili	229	—	Beans, beef	Tomato sauce	—	—
Dairy Queen: chili dog	330	—	Hot dog, beans	Tomato sauce	Roll	—
Long John Silver's Fish/More	894	—	Fish	French fries, coleslaw	Hush puppies	—
Arby's Ham'N Cheese	380	Cheese	Ham	Lettuce, tomato	Roll	—
Kentucky Fried Chicken Dinner	643	—	Chicken	Mashed potatoes, coleslaw	Roll	Gravy
McDonald's Egg McMuffin	327	Cheese	Egg, Canadian bacon	—	English muffin	—
Pizza Hut: pork and mushroom pizza	380	Cheese	Pork	Mushrooms, tomato sauce	Crust	—
Dairy Queen: banana split	540	Ice cream	Nuts	Banana	—	Whipped cream, strawberry topping, pineapple topping, chocolate syrup

Table 16-5. *(continued)*

Fast Food Item	Number of Calories	Milk Group	Meat Group	Fruit-Vegetable Group	Grain Group	"Others" Category
Dairy Queen: ice cream cone	150	Ice cream	—	—	—	Cone
Other desserts	240–250	—	—	—	—	Pies, cookies, turnovers, danish pastry
Side dishes (calories)		—	—	French fries (220), coleslaw (121), corn on the cob (169), mashed potatoes (64)	Roll (61), hush puppies (153)	Onion rings (270), gravy (23)
Beverages (calories)		Whole milk (150), 2% milk (120), McDonald's chocolate shake (383)		Orange juice (80)		McDonald's soft drinks (144), coffee (2)

Courtesy National Dairy Council: Fast Food: Junk? Gems? or Just OK? Rosemont, Ill, 1983.

Table 16-6. Meal #1: Hamburger, Fries, and Soft Drink (626 Calories).

Milk Group	Meat Group	Fruit-Vegetable Group	Grain Group	"Others" Category
—	Hamburger patty (124)	French fries (220)	Roll (119)	Soft drink (144) Catsup (8) Mustard (11)

Numbers in parentheses indicate calories.
Pros: This meal contains foods from three of the four food groups and has a moderate number of calories.
Cons: It does not contain any milk products. Milk provides the body with 50 or more nutrients needed for good health.
Courtesy National Dairy Council: Fast Food: Junk? Gems? or Just OK? Rosemont, Ill, 1983. Reproduced with permission.

minerals added, it can lead to electrolyte imbalance that can cause cardiac irregularities. It provides only 33 g of protein per day, far less than what the adolescent needs. The weight loss from this diet includes body fat as well as valuable body protein.

The Pritikin Diet

This is a very low fat, high carbohydrate diet. The carbohydrates come from vegetables, legumes, tubers, whole grains, and raw fruits. No degerminated grains or refined simple sugars are allowed. Protein is almost entirely from vegetable sources. The dieter is limited to 24 ounces of meat, fish, and poultry per week. Eight to 12 lb can be lost in a month on the 1200–1400 kcal plan and 12 to 14 lb per week on 600–800 kcal. The increased fiber and reduced fat, cholesterol, and sodium content of the diet make it difficult to follow for any length of time.

A weight reduction diet that provides essential nutrients would supply at least 1200 calories per day. At the same time, an exercise

regimen would be included. But the most important element of a good diet is that the dieter learns new eating habits that can be used throughout her lifetime. Groups such as Weight Watchers have helped adolescents lose weight without sacrificing nutrition. No adolescent, however, should ever diet below a calorie level recommended by her physician. Registered dietitians in hospitals, health departments, local dietetic associations, or in private practice can develop weight reduction plans that provide optimum nutrition for the adolescent.

Implications for Nutrition Education

Although a survey of 1300 high school students revealed that nutrition was of low interest when compared to other health subjects, they are indeed interested in their growth and weight.[49,50] Therefore, nutrition information given in health and science classes should be related to growth and development. The school cafeteria also can be used to teach nutrition.

As a future consumer, the adolescent needs more product information than is given in advertisements. Learning about food labeling and purchasing will help her make wise choices.

Media campaigns designed especially for the adolescent have been effective in providing nutrition information. Some examples include a fantasy comic book and a radio/television campaign using prizes and contests.[51,52] Similar programs that reach more adolescents should be designed.

Conclusion

Health professionals have a responsibility to the adolescent to help her reach her potential growth. Nutrition plays an integral part in this growth, and the adolescent needs to be aware of how her food intake and choices influence her future development.

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Sexually Transmitted Diseases 17

Major I. Keith Stone and Byron J. Masterson

As sexual mores have become more liberal, so has the incidence of sexually transmitted diseases in this country's children and adolescents.

Recent surveys of metropolitan area teenagers indicate the proportion of 15- to 19-year-old women who have had premarital sexual intercourse increased from 30% in 1971 to 50% in 1979.[1] The mean age at first intercourse was 16.2.[2] Figure 17-1 shows the reported incidence of gonorrhea in adolescent women between 1956 and 1979. During the same period that premarital intercourse increased by 66% (1971–78), the incidence of gonorrhea in women 15 to 19 increased from 600 per 100,000 to 1,500 per 100,000, a 250% increase.[3] Although the growth in reported cases of gonorrhea associated with the increased incidence of sexual intercourse among teenagers is only one measurable parameter of the changing sexual climate, it is indicative of the trend and the extent of the problem facing health care providers. Approximately 1 million women are treated for acute salpingitis in the United States every year.[4] There are 250,000 hospital admissions and 150,000 surgical procedures yearly as a result of acute salpingitis. The direct cost of treating this disease in this country is estimated at $700,000,000 annually.

If current trends continue, by the year 2000 there will be one episode of pelvic inflammatory disease (PID) and three physician visits for PID for every two women who reached reproductive age in 1970.[4] Fifteen percent of this group will have been hospitalized for the disease and more than half of these will have required major gynecologic surgery. If the current 20% risk of infertility after an episode of PID continues, 10% will be sterilized by PID and 3% will have an ectopic pregnancy.

Recognition of this dire forecast should prompt health care professionals to be particularly aware of the problem of sexually transmitted diseases in children and adolescents. Whereas emphasis has been traditionally placed on contraceptive education for this age group, we, as health care professionals, must realize the importance to both the individual and society of teaching our young people about the prevention and treatment of these currently epidemic diseases.

Gonorrhea

Neisseria gonorrhoeae was first isolated in 1879 by Albert Neisser. Prior to his isolation of the organism, history is filled with descriptions of a genital disease that we now know to be gonorrhea. Reported cases of gonorrhea in adolescent women approaching sexual maturity increased 300% between 1950 and 1975; between 1965 and 1975 the rate in 15- to 19-year-old females increased 500%.[3] Gonorrhea is primarily a disease of the young, the majority of infections found in those between 16 and 24. Although the incidence of the disease in males is highest in those 16 to 24, females most likely to have gonorrhea are under 14.[5]

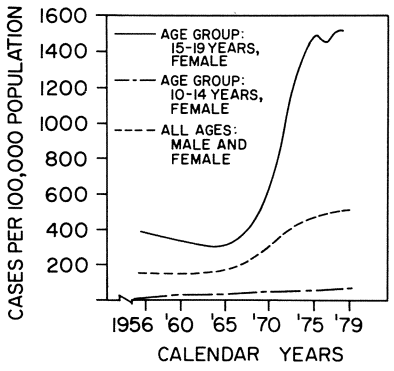


Figure 17-1. Incidence of reported gonorrhea among adolescent females, 1956–1979. From Shafer MB, Irwin CE, Sweet RH: Acute salpingitis in the adolescent female. Journal of Pediatrics 100(3):340, 1982. Reproduced with permission.

While the increased incidence of premarital sexual intercourse is responsible for much of the prevalence of gonorrhea in adolescents, there are additional factors. Surveys of adolescent females aged 15 to 19 in 1976 and 1979 have shown that as many as 66% of those who are sexually active use contraception irregularly or not at all,[1] and contraceptive methods appear to be an important factor in the prevention of gonorrhea. Those using barrier methods are less likely to develop infection because the condom and diaphragm obstruct the organism's access to the reproductive tract. Spermicidal foams and jellies that contain non-oxynol-9 or nonionic detergents also potentially prevent the spread of infection by their bactericidal activity.

The infecting organism is a gram-negative diplococcus, which usually infects only humans. It has a predilection for columnar and pseudostratified epithelium and is most commonly found in the urogenital tract. Growth under laboratory conditions requires a pH of 7.4, a temperature of 35.5 C, and a carbon dioxide atmosphere that varies between 2 and 10%.[5]

The majority of female patients who are infected with *N. gonorrhoeae* are asymptomatic; however, a significant number do complain of symptoms. The most common site of infection is the endocervical canal, and the patient may complain of a vaginal discharge. Other sites of infection that may prompt patients to complain are the urethra, periurethral glands of Skene, Bartholin's glands, and the upper genital tract. Gonococcal vaginitis is rare except in the very young or old. A prepubertal child with vaginitis caused by *N. gonorrhoeae* should be examined for sexual abuse. Depending upon sexual practices, pharyngitis and proctitis may be found. Disseminated disease may appear as polyarthritis, dermatitis, endocarditis, or meningitis.

An estimated 10–17% of women who have gonorrhea develop pelvic inflammatory disease.[6] In 47–66% the onset of pain occurs within 7 days of the menstrual period, which suggests that the gonococcus is disseminated at the time of menstruation from its usual endocervical columnar cell location into the uterine cavity and fallopian tube. *N. gonorrhoeae* can be isolated from the cervix in 20–80% of patients with acute salpingitis. In addition, the organism can be found in the fallopian tube or peritoneal cavity in 8–70% of patients with salpingitis whose cervical cultures yield *N. gonorrhoeae*.[7] These extremes may be because of gonorrhea's varying prevalence in different populations. In populations with a high prevalence of gonorrhea, most cases of acute pelvic inflammatory disease are associated with gonococcal infection. Where gonorrhea is less common, the organism is isolated from the cervix in fewer than half of all cases of PID. Moreover, the polymicrobial nature of pelvic inflammatory disease may explain the discrepancy in cervical and intraabdominal culture results. Sweet, in two different studies summarized by Shafer, noted that although 50% of their patients with acute salpingitis had *N. gonorrhoeae* in the endocervix, the organism could be recovered from the fallopian tube in only 23%.[3] Anaerobic bacteria were the most frequent fallopian tube isolates from patients with acute salpingitis. It is probable that as the disease progresses the microflora of the fallopian tube may change from *N. gonorrhoeae* to secondary invaders from the lower genital tract. Patients admitted to the hospital after several days of symptoms already may have passed through the initial gonococcal stage. Sweet was able to show that 70% of patients presenting within the first 24 hours of the onset of symptoms had *N. gonorrhoeae* isolates, whereas after 24 hours there was a shift in

isolates to anaerobic bacteria and uneaplasma.[8] After 48 hours gonococci were isolated in only 1%. Aerobes and anaerobes in the fallopian tubes during the initial stage of infection seem to indicate that organisms other than the gonococcus may initiate the disease.

As an initiator of salpingitis and pelvic inflammatory disease, the gonococcus attaches to mucosal epithelial cells, penetrates the cells, and causes cell destruction. Destruction of the endosalpinx results in a purulent exudate that exudes from the fimbriated end of the tube and results in pelvic peritonitis. Contiguous structures such as the ovary, omentum, and bowel may become involved.

Symptoms associated with classic salpingitis include lower abdominal pain, vaginal discharge, gastrointestinal problems, abnormal uterine bleeding, fever, and chills. Recent studies using laparoscopy have shown that the diagnosis of acute salpingitis using these criteria often is inaccurate. Jacobson and Weström were able to confirm salpingitis in only 65% of 814 patients who underwent laparoscopy to substantiate the diagnosis.[9] Approximately 23% of the study group had normal pelvic findings and the remaining 12% had other pelvic pathology such as appendicitis, endometriosis, ectopic pregnancy, and ruptured ovarian cysts. There was no significant difference in the symptoms of patients with normal pelvic exams and those with confirmed salpingitis. Both groups had a similar incidence of lower abdominal pain, increased vaginal discharge, irregular bleeding, urinary symptoms, and gastrointestinal symptoms. The only significant difference was a history of fever and chills in 40% of patients with confirmed salpingitis. Evaluation of clinical signs and laboratory data did reveal significant increases in the incidence of adnexal tenderness, fever, and abnormal vaginal discharge in patients with visually confirmed salpingitis. However, the overlap was so large that these factors could not be relied upon for diagnosis. Only 33% of those with visually confirmed salpingitis had a fever. In addition, only 20% had the classical symptom constellation of abdominal pain and tenderness, cervical motion tenderness, adnexal tenderness, fever, leukocytosis, and elevated erythrocyte sedimentation rate. Subsequent investigators have pointed out that the visually normal group may have harbored infection that was confined to the mucosa of the fallopian tube and/or endometrium. The 17% rate of isolation of *N. gonorrhoeae* from Jacobson and Weström's visually normal group supports this contention.[9] Obviously not all patients with a presumed diagnosis of salpingitis can or should be laparoscoped. But Jacobson and Weström have demonstrated the wide spectrum of the disease and made clinicians acutely aware that the diagnosis of salpingitis often is inaccurate. Given the diversity of presenting symptoms, the clinician must remember that the sexually active adolescent who has lower abdominal pain and no fever is not excluded from having PID. A cavalier approach to her symptomatology may result in tubal scarring and infertility.

To diagnose gonococcal infection, specimens may be obtained from the endocervical canal, the urethra, and the rectum. If culdocentesis or laparoscopy is necessary when salpingitis is suspected, peritoneal fluid can be used for a Gram's stain and culture. Gram's stain can be useful in the initial evaluation, but one must remember that polymorphonuclear leukocytes must be present for the diagnosis, and gram-negative diplococci must be found within the polymorphonuclear cell. Sensitivities of Gram's stain range from 48 to 71%, although specificity is 97–100%. In evaluating adolescents and children, Wald noted a Gram's stain specificity of 99% (number of negative stains/number of negative cultures for patients with a negative culture × 100%) and a sensitivity of 65% (number of positive stains/number of positive cultures for patients with a positive culture × 100%).[10] These characteristics make Gram's stain a poor choice for screening a population with a low incidence of gonorrhea. When the prevalence is low, the number of false positives approximates the number of true positives and the positive predictive value is low. Those suspected of having acute pelvic inflammatory disease have a high prevalence of cervical gonorrhea, thereby reducing the number and proportion of false-positive Gram's stains and increasing the reliability of a positive Gram's stain.

The isolation and identification of *N. gonorrhoeae* by culture is the most specific method of making the diagnosis. The medium most often used is a chocolate agar base with

additives for nutritional requirements and prevention of overgrowth of contaminating microorganisms. Direct plating and the use of an on-site laboratory will increase the yield of culture diagnosis. The major drawback of culturing is the time, 24–48 hours from the time the specimen is obtained until growth is seen, and an additional 24 hours for the confirmatory reaction. Studies are underway to evaluate the applicability of antigen assays. The specificity and sensitivity of the assay along with a diagnosis within 24 hours may make the antigen assay our future mainstay.

Treatment should be initiated once gonorrhea is diagnosed. The recommended regimens for treating uncomplicated infection are listed in Table 17-1.[11] Children who weigh less than 100 lb can be treated at one visit with oral doses of amoxicillin, 50 mg/kg, and probenecid, 25 mg/kg (maximum 1.0 g). An alternative regimen is aqueous procaine penicillin G, 100,000 units/kg intramuscularly (IM), and probenecid by mouth, 25 mg/kg (maximum 1.0 g). Neonates with gonococcal opthalmia should be hospitalized and isolated for 24 hours following therapy. Untreated gonococcal ophthalmia is highly contagious and may rapidly cause blindness. Aqueous pencillin G, 50,000 units/kg/day, intravenously (IV) in two doses, should be given for 7 days. Eyes should be irrigated immediately with saline or buffered ophthalmic solutions and then at least at hourly intervals as long as a discharge persists.

Spectinomycin or cefotaximine sodium should be given when penicillinase-producing *N. gonorrhoeae* are isolated. Neonates with ophthalmia as a result of this organism should be treated with cefotaximine or gentamicin. Children who are allergic to penicillin should be treated with spectinomycin, 40 mg/kg IM. Children older than 8 may be treated with oral doses of tetracycline, 40 mg/kg/day in four divided doses for 5 days.

Coexisting chlamydial infection has generated concern. Chlamydial infection has been documented in up to 45% of gonorrhea patients who have had adequate cultures.[11] The Centers for Disease Control currently are investigating the advisability of administering a combined regimen for the uncomplicated gonorrhea patient who may be harboring a coexistent chlamydial infection. This regimen consists of oral doses of amoxicillin, 3.0 g, or ampicillin, 3.5 g (either with 1.0 g probenecid), and tetracycline, 500 mg, given orally four times a day for 7 days.

In addition to those patients who have laboratory-confirmed gonorrhea, the Venereal Disease Control Division of the Centers for Disease Control advises treating those persons who are known to have been recently exposed to gonorrhea. If culture alone is used, 12–30% of the women seeking treatment because of exposure would be infected yet go untreated.[12]

Table 17-1. Uncomplicated Infection in Adolescents (Weighing 100 lb or Greater).

Recommended Regimens (the order of presentation does not indicate preference)

Tetracycline HCl: 500 mg by mouth, 4 times a day for 7 days (total dose 140 g). Other tetracyclines are not more effective than tetracycline HCl. All tetracyclines are ineffective as a single-dose therapy. Doxycyline hyclate, 100 mg by mouth twice a day for 7 days, may be substituted for tetracycline.

Advantage	Disadvantages
1. Effective against co-existing chlamydial infections	1. Requires compliance with multiple doses 2. May encourage the emergence of tetracycline-resistant strains if the regimen is not strictly followed 3. Ineffective against anorectal gonococcal infections in men

Amoxicillin/ampicillin: Amoxicillin, 3 g, or ampicillin, 3.5 g, either with 1.0 probenecid by mouth

Advantage	Disadvantages
1. Single-dose treatment	1. Ineffective against chlamydial infections 2. Ineffective against anorectal and pharyngeal gonococcal infections

Aqueous procaine penicillin G: 4.8 million units injected IM at 2 sites with 1.0 g probenecid by mouth

Advantage	Disadvantages
1. Single-dose therapy	1. Injection 2. Possible procaine reaction 3. Possible penicillin anaphylaxis 4. Ineffective against chlamydial infections

From Sexually transmitted diseases treatment guideline 1982. Morbidity and Mortality Weekly Report (Supplement) 31(25):375, 1982. Reproduced with permission.

The combination of Gram's stains and cultures would lower the incidence of women who are infected and untreated to 4–20%. Based on these numbers it is advised that persons exposed to gonorrhea should be examined, cultured, and treated immediately. Infants born to mothers with gonorrhea are at high risk for infection and should be treated with a single injection of aqueous crystalline penicillin G, 50,000 units IM or IV for term babies or 20,000 units IM or IV for low-birth-weight infants.

The progression of *N. gonorrhoeae* from the cervix into the upper genital tract may result in polymicrobial salpingitis and pelvic inflammatory disease. Given the spectrum of coexisting organisms, it is not feasible to treat the disease as a pure infection and therapeutic regimens should cover *N. gonorrhoeae*, (*chlamydia trachomatis*, anaerobic bacteria (including Bacteroides and gram-positive cocci), facultative gram-negative rods (*Escherichia coli*), *Actinomycosis israeli*, and *Mycoplasma hominis*. Hospitalization should be strongly considered when the diagnosis is uncertain, and/or when the patient is pregnant, is an adolescent, has an IUD, is unable to follow an outpatient regimen, fails to respond to outpatient therapy, has a suspected pelvic abscess, or has signs of a peritoneal infection.

The long-term goals in managing acute salpingitis are to prevent infertility and the chronic residue of infection. Prior to the widespread use of antibiotics, acute salpingitis, with few exceptions, was a self-limited disease from which many women recovered. But infertility rates were greater than 50%.[3] With current antibiotic therapy, however, Swedish studies have shown that patients who had had at least one episode of salpingitis have a 21% infertility rate compared to a 3% rate for a control population.[9] Patients with gonococcal salpingitis had a better prognosis for fertility than did those with nongonococcal disease. This may be because patients with gonococcal salpingitis present with more florid disease, are admitted earlier, and are treated with intravenous antibiotics. Patients treated within 2 days of onset had patent oviducts on hysterosalpingogram, according to Viberg.[13] When treatment was delayed for 7 days or longer 30% had tubal obstruction. For economic and logistic reasons, most patients in the United States are treated as outpatients for salpingitis. A recent six-hospital collaborative study of ambulatory regimens found that of 240 patients with salpingitis and a positive gonococcal culture from the endocervix, 13.8% were treatment failures.[14] In non-gonococcal salpingitis, the overall failure rate reached 17%.

The adolescent female presents a particular problem in considering outpatient vs. inpatient therapy. Shafer et al believe that psychosocial factors are so important that the adolescent should be hospitalized. Acute salpingitis recognized as a sexually transmitted disease can be so emotionally traumatic that it may be difficult for the patient to follow prescribed care if left to her own devices.[3] The threat of infertility, although real and a source of future concern, is not seen by the adolescent patient as immediate and important.

The Center for Disease Control notes that the treatment of choice in acute pelvic inflammatory disease has not been established.[11] In determining the regimen, broad spectrum coverage is mandatory. Those adult-weight patients treated as outpatients may be given cefoxitin, 2.0 g IM, amoxicillin, 3.0 g by mouth, ampicillin, 3.5 g by mouth, or aqueous procaine penicillin, G, 4.8 million units IM at two sites; these should be given with probenecid, 1.0 g by mouth. Each of these regimens should be followed by doxycycline, 100 mg orally twice daily for 10–14 days. Combined cefoxitin and doxycycline are active against *N. gonorrhoeae*, including penicillinase-producing strains and *C. trachomatis*. If outpatient therapy is selected the patient should be reevaluated in 48 to 72 hours and should be hospitalized if she is not responding to treatment.

Those adult-weight patients meeting the criteria for inpatient therapy may be treated with doxycycline, 100 mg IV twice daily, and cefoxitin, 2.0 g IV four times daily. Children older than 3 months should not receive more than 12 g of cefoxitin daily and the dose should be based on 80–160 mg/kg in four to six equal doses. Children over 8 years of age weighing less than 100 lb may receive doxycycline on the first day of treatment at 2 mg/lb of body weight in one or two infusions. Subsequent daily dosage is 1–2 mg/lb. Therapy should be continued intravenously for at least

4 days and at least 48 hours after the patient defervesces. Doxycycline should be continued orally twice a day after discharge for 10 to 14 days. An alternative regimen consists of clindamycin, 600 mg IV four times daily, and gentamicin or tobramycin, 2.0 mg/kg IV, followed by 1.5 mg/kg IV three times daily in adult-weight patients with normal renal function. Again, the drugs should be continued for at least 4 days and 48 hours after the patient defervesces. Potential toxicity always must be kept in mind. It also should be noted that the latter regimen provides coverage against anaerobes and facultative gram-negative rods but may not provide the best activity against *C. trachomatis* and *N. gonorrhoeae*. If the patient has an IUD, therapy should be initiated before attempting to remove it.

Follow-up cultures are recommended for all patients 4 to 7 days after therapy is completed. Attempts should be made to examine and treat all those who have had sexual contact with persons treated for gonorrhea. Efforts also should be made to teach the adolescent female about the epidemiology, prevention, therapy, and prognosis of her disease. The rapport established during this crisis may prevent her from joining the ranks of those who have had three or more episodes of salpingitis and have a 54% incidence of infertility.[15]

Chlamydia

There are an estimated 3 million chlamydial infections annually in the United States, making *Chlamydia trachomatis* the leading cause of sexually transmitted diseases.[16] The organism exists as 15 recognized serotypes.[17] Three of the serotypes (L1, L2, and L3) represent the agents causing lymphogranuloma venereum. Serotypes A, B, Ba, and C are responsible for trachoma. The eight remaining serotypes, D, E, F, G, H, I, J, and K, are responsible for inclusion conjunctivitis, newborn pneumonia, urethritis, cervicitis, epididymitis, salpingitis, acute urethral syndrome, and perinatal infections. Although chlamydia are capable of metabolic activity, they do not have an ezyme system capable of generating ATP, and hence are obligatory intracellular bacteria. After attachment to the host cell, the microorganism is ingested by phagocytic activity.[18] The entire intracellular life cycle is spent in the phagosome, dividing and organizing into infectious elementary bodies. In 48–72 hours the host cell bursts, liberating the infectious particles. Although they resemble bacteria with their rigid cell wall, DNA and RNA content, susceptibility to antibiotics, and multiplication by binary fission, their obligatory intracellular existence suggests viral properties.

Several clinical conditions in the female have been attributed to chlamydia, including cervicitis, salpingitis, urethral syndrome, urethritis, and perinatal infections. From 20 to 40% of sexually active women have microimmunofluorescent chlamydia antibody titers; yet most do not have active infection. Chlamydia have been found in 15–33% of patients examined in venereal disease clinics, in 29–68% of women who are sexually intimate with men who have nongonococcal urethritis, in 67–74% of women whose partners have culture-confirmed urethritis as a result of chlamydia, and in 34–63% of women with mucopurulent endocervicitis.[16] As many as 5% of sexually active women carry chlamydia in their cervices. Within this population there are certain groups with a greater risk of carrying the disease. Young, unwed mothers often have high cervical infection rates, as do women who use oral contraceptives, those with cervical ectopy, and women who are partners of men with nongonococcal urethritis. Schachter noted a carrier rate for asymptomatic women of 3.5% for chlamydia, 0.5% for herpes, and 0.4% for gonococci. In symptomatic women the isolation rate increased to 15% for chlamydia, 5.3% for herpes, and 4.7% for gonococci.[19] The majority of women infected with chlamydia go untreated because the infection is asymptomatic or inapparent.

The cervix is the most common genital site colonized with chlamydia. The infected cervix may range from clinically normal to severely eroded with mucopurulent discharge. Reese noted that only two organisms—*C. trachomatis* and *N. gonorrhoeae*—are associated with chronic cervicits and mucopurulent cervical discharge.[20] The urethra is another common site of infection. In patients with acute urethral syndrome or dysuria and frequency in association with sterile cultures, 25% may be infected

with chlamydia.[21] While most of the isolates in these patients were from the cervix, 40% were from the urethra. It must be remembered that because chlamydia is an obligate intracellular organism, the bacterium does show up in urine cultures; therefore urethral swabs are necessary.

Increasingly, chlamydia are being implicated in salpingitis. Scandinavian investigators have implicated chlamydia in approximately 50% of cases of acute salpingitis. Mårdh notes that 75% of patients with chlamydia-associated salpingitis are under 25.[22] Patients complain of pelvic pain and increased vaginal discharge. Febrile illness is significantly less frequent than in those with gonococcal salpingitis. The erythrocyte sedimentation rate is higher in chlamydial salpingitis than in gonococcal or nongonococcal-nonchlamydial salpingitis. In the United States, the role of chlamydia in salpingitis is not as well defined as in Scandinavia. The organism is recovered much less frequently in laparoscopic studies. Sweet and his colleagues did not isolate chlamydia from oviductal exudates in 37 women who underwent laparoscopic examination for confirmed salpingitis.[23] Eschenbach recovered chlamydia from intraperitoneal sites only once in a series of 102 patients.[24] The inability to isolate the organism may stem from the relative inaccessibility of the intracellular bacterium. But indirect evidence to support the role of chlamydia in salpingitis does exist. Eschenbach was able to document a fourfold rise in serum antibodies against chlamydia in 20% of patients with acute salpingitis.[24] Bowie has reported recovering chlamydia from the cervix of 50% of women diagnosed with PID compared to finding the organism in only 20% of women attending a venereal disease clinic without a diagnosis of salpingitis.[25] Direct evidence of salpingitis as a result of chlamydia has been documented by Ripa in monkeys innoculated with the organism.[26]

Chlamydial infection may present in the newborn as a mucopurulent discharge developing 5 to 14 days after birth. It is the most common cause of conjunctivitis in the first month of life.[27] The infection most often resolves spontaneously in the first few months; however, some infants have persistent conjunctivitis and subsequent conjunctival scarring. The disease starts with a watery discharge that rapidly becomes purulent. The eyelids are red and swollen. Typical inclusion bodies may be found on Giemsa stain and chlamydia are readily cultured from the eye. In 1977, chlamydial pneumonia was described in infants and now is recognized as one of the three most common pneumonias in infancy. The disease presents between the fourth and 11th week and in 50% of cases begins as upper respiratory congestion in association with bulging eardrums. As the disease progresses, tachypnea and a prominent cough may occur. Radiographically there is hyperexpansion of the lungs with bilateral symmetric interstitial infiltrates.

Both conjunctivitis and pneumonia are serious complications in the infant. There are more than 155,000 infants born in the United States each year who are exposed to chlamydial infections;[28] 100,000 will become infected. There are 75,000 cases of conjunctivitis and 30,000 cases of pneumonia annually. Concern about chlamydial infections in the newborn has prompted discussion on efforts to prevent colonization in infants. Although the routine culturing of expectant mothers is expensive, it may be justified in selected high-risk groups. Schachter and Grossman have noted that in populations with greater than 6% cervical infection rates, the costs of treating the infected infants far exceeded the cost of identifying and treating pregnant women to prevent prenatal exposure.[29] Because selected groups of at-risk patients have colonization rates of 15–30%, it seems advisable to incorporate prenatal screening and therapy in these groups. A less controversial measure that can be used to prevent chlamydial conjunctivitis is topical erythromycin ointment applied at birth. Silver nitrate does not prevent chlamydial conjunctivitis. In addition to its protection against chlamydial conjunctivitis, erythromycin also is effective in preventing gonococcal ophthalmia neonatorum.[16]

The diagnosis of chlamydial infection is hampered by the difficulty in culturing the organism. Adequate samples of epithelial cells must be obtained to culture chlamydia; culturing a discharge is insufficient. Perhaps for this reason many clinical studies of infected patients have failed to identify the organism. Recently two simple tests have been marketed to assist in diagnosing chlamydial infections.[30]

One breaks down epithelial cell walls and uses antibodies to detect chlamydial antigens on the surface of exposed organisms or extracellular elementary bodies. The other assay detects the organism with a fluorescein-labeled monoclonal antibody. While most hospitals do not have the ability to culture chlamydia, they do have the equipment needed to perform the new assays, both of which can be done in less than 3 hours. The epithelial wall enzyme test has shown 88% sensitivity and 97% specificity, and the fluorescein test has demonstrated 95% sensitivity and specificity. Although further experience is needed, these assays may revolutionize the ability to diagnose and treat *C. trachomatis*.

The Centers for Disease Control recommend the following therapy for culture-proven chlamydial infections: for uncomplicated urethral, endocervical, or rectal infection in older adolescents, tetracycline HCI, 500 mg by mouth four times daily for 7 days, or doxycycline, 100 mg twice daily for 7 days;[11] children above age 8 should receive tetracycline 25–50 mg/kg/day in four divided doses. For the patient who cannot use tetracycline, prescribe erythromycin, 500 mg by mouth four times daily for 7 days; for the newborn with established chlamydial conjunctivitis, a dosage of erythromycin syrup, 50 mg/kg/day in four divided doses for at least 2 weeks; for infants with established lower respiratory disease due to chlamydia, a dosage of erythromycin syrup, 50 mg/kg/day in four divided doses for at least 3 weeks.

When culture facilities are not available and nongonococcal urethritis or nongonococcal mucopurulent cervicitis is diagnosed, the therapy is the same as outlined for culture-proven chlamydial infection. Sexual contacts should be examined and treated for exposure to *C. trachomatis* with one of the above regimens.

Herpes

Herpes simplex virus is the second most prevalent sexually transmitted disease in the United States today.[31] Figure 17-2 shows the escalating trend of this enigmatic disease. The marked increase in physician consultations between 1966 and 1979 represents only a portion of those patients with the disease because many do not seek medical help. Some estimates put the number of herpes victims as high as 20 million.[32] At sexually tranmsitted disease clinics, herpes accounts for 3.4% of visits by men and 1.5% of visits by women.[33]

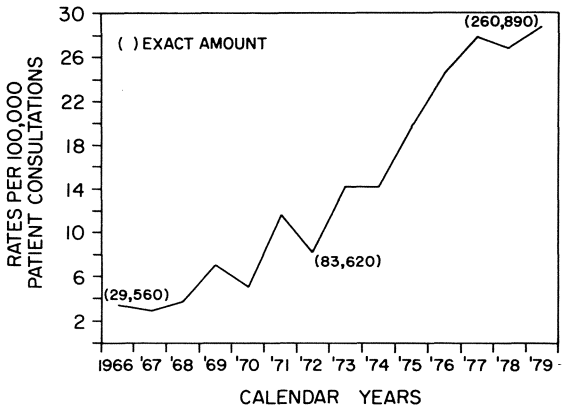


Figure 17-2. Estimated rates of patient consultations with private physicians for genital herpes infection, United States, 1966–1979. From Centers for Disease Control: Genital herpes infection, United States, 1966–1979. Morbidity and Mortality Weekly Report 31:137, 1982. Reproduced with permission.

Herpes, a Greek word, means "to creep." It was first used by Thomas Bateman in 1814 to describe skin lesions in the genital region.[34] The herpes virus was discovered in 1912 and isolated from the female genital tract in 1946. The five viruses that cause herpeslike infections in the human are herpesvirus type 1(HSV-1), herpesvirus type 2, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus. Genital herpes may be caused by either herpesvirus. Although there are antigenic differences between the two types of virus, they cannnot be structurally differentiated. Both are large DNA viruses consisting of a nucleocapsid that is surrounded by a lipid envelope containing glycoproteins. Nucleic acid sequences reside within the DNA molecule and determine the enzymatic differences between these two viral particles. It has been estimated that as many as 50% of these sequences differ between HSV-1 and HSV-2.[35] Clinically, HSV-2 is more frequently implicated in genital disease; however, HSV-1 may be responsible for 15% of primary genital herpes.[36]

There are three clinical syndromes caused by herpesvirus in the genital region. A primary

genital infection in a patient without circulating antibodies to HSV-1 or HSV-2 is a first-episode primary genital herpes. If antibodies are present from a prior infection elsewhere, the disease is a first-episode nonprimary. The third syndrome, recurrent herpes, occurs in a patient who has had a prior episode of genital herpes and now has the latent virus activated.[35]

First-episode primary genital herpes results when the virus is transmitted through direct contact, either genital-genital or oral-genital. The incubation period averages 6 days with a range of 2 to 20 days.[34] Symptoms may include severe pain in the genital region, rectal pain or burning, dysuria, and frequent urination. Low-grade fever, headache, and malaise are systemic symptoms. Lesions may be found on the external genitalia, vagina, cervix, rectum, urethra, mucosa of the bladder, buttocks, and thighs. Initial local redness will progress to vesicles that rupture, producing shallow, painful ulcers. Healing usually is complete in 20 days but may take up to 6 weeks; the mean duration of viral shedding is 10 days.[37] The ability to isolate the virus from the cervix is high in this group of patients, with investigators reporting rates as high as 85%.[38] During the primary infection the virus migrates through peripheral nerves to the sacral ganglia where it is undetectable. Since the virus ascends in the protected intraaxonal space, it is not exposed to antibodies and hence they appear to play only a minor role in limiting the migration.[34] The virus then becomes dormant.

Reactivation of the dormant virus results in local disease that is very similar to a first-episode nonprimary infection. In both states, circulating neutralizing antibodies play a significant role in whether the disease develops. Recurrent disease occurs more often after HSV-2 primary infections and the probability of recurrence is directly related to the presence of HSV-2 neutralizing antibody.[36] Symptoms usually are mild and local, lasting approximately 7 days. Complete healing requires 10 days and viral shedding occurs for only 4 days. The factors that stimulate reactivation are poorly defined but are thought to include emotional stress, physical stress, fever, sexual activity, and menstrual onset.

Local complications of the disease range from secondary bacterial infection to urethral and bladder infection with subsequent urinary retention that requires catheterization. Of primary concern is the transfer of herpesvirus to the fetus during its passage through an infected genital tract. Approximately 80% of these infected infants either die or develop major neurologic deficits.[39] Whitley found that in approximately 50% of pregnancies that resulted in the birth of an infected infant, delivery was preterm and 70% of mothers were asymptomatic.[40] Neonatal herpes was disseminated in two-thirds of cases and involved the adrenals, liver, lungs, and central nervous system. The remaining third had local disease of the skin or eyes.[41] Current obstetric practice dictates a cesarean section to prevent direct contact with the infecting organism in those with positive herpes virus cultures or active lesions at term or onset of labor.

The long-term sequelae of genital herpes are poorly defined. Controversy exists over the role of herpesvirus in cervical dysplasia and carcinoma. Although investigators have shown that 60% of human cervical tumors contain HSV, DNA, and RNA,[42] it is unclear whether there is a causal relationship or whether the coexistence of herpes virus and carcinoma are merely unrelated reflections of a patient's sexual habits. Until this relationship is defined, it is advised that the pediatric or adolescent patient who has a history of genital herpes have a yearly Pap test to detect neoplastic processes.

The diagnosis of herpes frequently is made based upon the characteristic clinical picture of the lesion. The virus can be isolated in approximately 80% of cases.[43] Direct immunoperoxidase assays demonstrate the virus in 66% of cases and direct immunofluorescence in 55%. Cytologic testing has a high rate of false negatives, with studies showing positive cytologic results in only 38–50% of patients with suspected herpes compared to positive cultures in 80% of the same patients.[38]

Treatment of first-episode primary disease is aimed to ameliorating the symptoms and reducing the duration of the infection. There is no cure for herpes. Physicians may prescribe Acyclovir ointment 5%, applied locally every 3 hours for 7 days.[11] Therapy should be

initiated as soon as possible following the onset of signs and symptoms. Viral shedding and disease duration are reduced if therapy is started within 6 days of the onset of symptoms. This drug has not been approved for pregnant women. Analgesics, antiinflammatory agents, and sitz baths in povidone iodine solutions can be used as supportive therapy. Urinary retention should be treated with catheterization and urinary antiseptic coverage. There is no effective therapy to shorten the duration of recurrent disease. Supportive therapy should be offered, and patients made aware of the risk of infectivity while the disease is active. The risk of transmission during the asymptomatic stage is unknown. Adam reported virus shedding from the cervix in five of 50 asymptomatic women and up to 6 months after they presented with active genital herpes.[44]

Syphilis

Syphilis is the third most common reportable infectious disease of adolescence, surpassed only by gonorrhea and varicella.[45] In the United States there were 27,204 cases in 1980 compared to 20,399 in 1977, a 33.4% increase.[46] Of the sexually transmitted diseases, syphilis has for centuries drastically altered the course of individual and national destinies. It raged as an epidemic in Europe in the 15th and 16th centuries, causing thousands of deaths. No respecter of social boundaries, it afflicted upper as well as lower classes. The deaths of such prominent historical figures as Peter the Great and Sir Randolph Churchill have been attributed to advanced syphilis.[47,48] Only with the advent of antibiotic therapy have we had the ability to cure and arrest the spread of syphilis. The increasing incidence of the disease is a reflection of an alteration in our societal sexual mores. Although we do not anticipate an epidemic comparable to those of the past, any increase in this potentially fatal disease should be viewed with grave concern.

Treponema pallidum, the spirochete responsible for syphilis, is sensitive to drying and heat. It survives best in the moist and warm oral and anogenital tracts. The disease is recognized in several distinct stages. Primary syphilis is noted within 10 to 90 days after contact with an infectious source. Typically, a painless indurated ulcer with raised borders will appear in the genital region; however, spontaneous healing may occur before the patient consults a physician. Additionally, the lesion may occur in regions that do not raise suspicion such as the nipple, the oropharynx, the vagina, the cervix, and the anorectal area.[49] If the ulcer heals without adequate therapy, the disease will appear again in 6 weeks to 6 months. Systemic symptoms such as malaise, fever, headache, and sore throat may occur. A generalized adenopathy may be present in association with a variety of skin lesions (reddish/bronze papulomacular lesions often marked on the palms and soles). Condylomata and mucous patches may be seen. Occasionally, the disease may result in hepatitis, meningitis, periostitis, and the nephrotic syndrome. Without therapy the disease becomes dormant or latent, during which time it may relapse as secondary syphilis for up to 4 years. Twenty-five percent of patients who have not been adequately treated will then progress to tertiary syphilis,[49] manifested as acute or subacute meningitis, cerebrovascular accidents, transverse myelitis, aortic aneurysm, or aortic insufficiency.

Congenital syphilis presents a particular problem for the perinatologist and the pediatrician. Dissemination of the spirochete from the infected mother to the fetus is possible at all stages of maternal infection and all stages of gestation. Although it was once believed that the spirochete could not cross the placental barrier before 16 weeks, infected abortuses have been described at 9 and 10 weeks of gestational age.[50] Fetal infection may result in intrauterine death, intrauterine growth retardation, and premature labor. Neonatal infection may occur as early or late disease. Early congenital syphilis may be associated with hemolytic anemia, periostitis, osteochondritis, meningitis, rhinitis, and dermatitis consisting of infectious bullous vesicular eruptions.[49] Late congenital syphilis is associated with periostitis of the frontal and parietal bones, short maxilla, abnormal dental development, interstitial keratitis, and eighth nerve deafness.

The diagnosis of syphilis depends on micro-

scopic and serologic studies. Darkfield examination of material from moist lesions will be positive for the spirochete in primary syphilis and in most lesions of secondary syphilis. Serologic tests consist of the Venereal Disease Research Laboratories (VDRL) test and the rapid plasma reagin (RPR) test. These tests measure reagin, a nonspecific gamma globulin. They usually become positive 1 or 2 weeks after the chancre has formed. A negative test does not exclude syphilis, since initial seronegative syphilis occurs in 50% of patients with primary syphilis, 1% of those with secondary syphilis, and 30% of patients with late tertiary syphilis.[45] False-positive results can occur with mononucleosis, hepatitis, pneumonia, lupus erythematosus, rheumatoid arthritis, sarcoidosis, and many bacterial and viral infections.[49] Although these tests are used for screening, confirmatory serologic testing is done with either the treponema immobilization (TPI) test or the fluorescence treponema antibody absorption (FTA-ABS) test. These treponemal antigen assays are highly specific and sensitive, and false positives are extremely rare. The FTA-ABS will be positive in approximately 80% of those with primary syphilis. These tests do not differentiate active from past infection and may remain positive for long periods.

The therapy for early syphilis (primary, secondary, and latent—less than 1 year's duration) in adult-weight adolescents is benzathine penicillin G, 2.4 million units IM,[11] preceded by 1 g probenecid, 30 minutes before penicillin. Patients who have a penicillin allergy should be treated with tetracycline HCL, 500 mg orally four times a day for 15 days. For syphilis greater than 1 year's duration (except neurosyphilis), administer benzathine penicillin G, 2.4 million units IM weekly for 3 weeks (7.2 million units total). Patients allergic to penicillin should receive tetracycline, 500 mg orally four times daily for 30 days. Cerebrospinal fluid should be analyzed in patients with signs or symptoms that would suggest neurosyphilis and in those with syphilis of longer duration than 1 year. Therapeutic regimens for neurosyphilis include aqueous crystalline penicillin G, 12–24 million units IV per day (2–4 million units every 4 hours) for 10 days, followed by benzathine penicillin G, 2.4 million units IM weeky for 3 doses; 10 days of aqueous procaine penicillin G, 2.4 million units IM daily, and probenecid, 500 mg by mouth four times daily, followed by benzathine penicillin G, 2.4 million units IM weekly for three doses; or benzathine penicillin G, 2.4 million units IM weekly for three doses.

Infants with congenital syphilis should have a cerebrospinal fluid examination before the start of therapy. Symptomatic infants or asymptomatic infants with abnormal cerebrospinal fluid should receive aqueous crystalline penicillin G, 50,000 units/kg IM or IV daily in two divided doses for a minimum of 10 days. An alternate regimen is aqueous procaine penicillin G, 50,000 units/kg IM daily for a minimum of 10 days. Asymptomatic infants with normal cerebrospinal fluid should receive benzathine penicillin G, 50,000 units/kg IM in a single dose. After the neonatal period, penicillin therapy for congenital syphilis should utilize the same doses as for neonatal congenital syphilis. For larger children the total dose of penicillin need not exceed that used in adult syphilis of more than 1 year's duration. After the neonatal period, the dose of tetracycline for congenital syphilis in patients who are allergic to penicillin should be individualized but need not exceed that used in adult syphilis of more than 1 years' duration. Do not use tetracycline in children under 8.

As many as 60% of adolescents with early syphilis will have transient febrile reactions after penicillin treatment (Herxheimer reaction).[45] Temperature elevations and accompanying headaches are mild and may be treated with aspirin. All patients should be followed with serologic testing at 3, 6, and 12 months to evaluate the adequacy of therapy for early and congenital syphilis. Retreatment should be considered if clinical signs or symptoms recur, e.g., there is a fourfold increase in titer with a nontreponemal test, or a nontreponemal test showing a high titer fails to demonstrate a fourfold decrease within a year of therapy.[11] Patients with syphilis of duration greater than 1 year should have repeat serologic testing 24 months after treatment, and those with neurosyphilis must be followed with periodic serologic testing, clinical evaluation at 6-month intervals, and repeat CSF examinations for at least 3 years.

Condyloma Acuminata

Venereal warts or condyloma acuminata in the adolescent are almost invariably transmitted sexually. The same papilloma virus responsible for condyloma acuminata causes common warts (verruca vulgaris) and juvenile warts (verruca plana).[51] As with other sexually transmitted diseases, the prevalence of the infection is directly related to the sexual activity of the population. As would be expected, there has been an increasing number of cases of condyloma.[52]

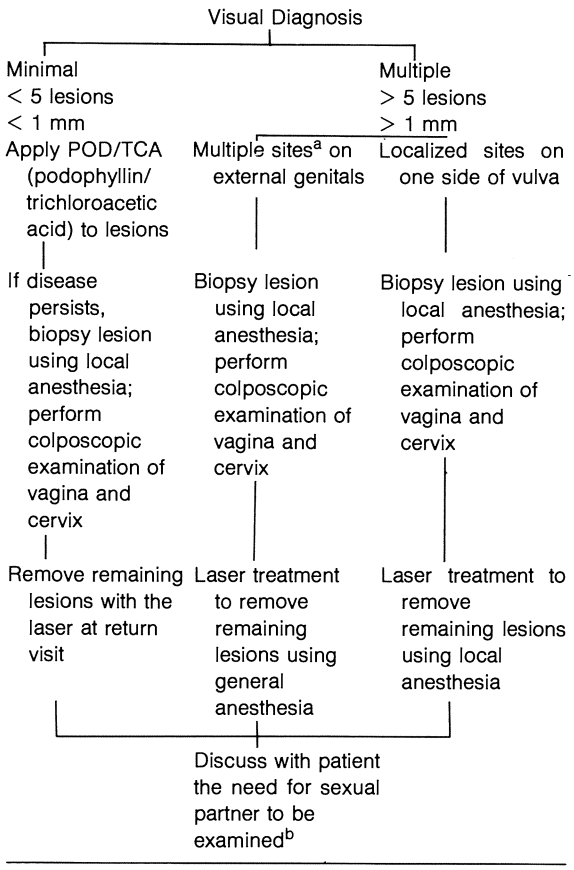
Approximately 65% of sexual partners of those with condyloma develop the disease within 3 to 4 months following contact. Usually the lesion appears within 4 to 12 weeks after exposure; however, the incubation period is variable.[53] The typical lesion is sessile and wartlike with a vegetative appearance. The lesion may be noted on the external genitalia, anorectal region, urethral meatus, and within the vagina, where it may be present on the cervix. Frequently a vaginal discharge occurs, which may be caused by concurrent sexually transmitted organisms.

The diagnosis typically is made on the basis of the appearance of the lesion. When uncertain, a biopsy is indicated. The typical microscopic appearance of condyloma is that of papillomatosis, acanthosis, elongation of the rete pegs, parakeratosis, and cytoplasmic vacuolization.[54]

Therapeutic regimens have been less than optimal. Current recommendations advise an application to the wart of podophyllin 10–25% in compound tincture of benzoin, followed by thorough washing in 1–4 hours. Podophyllin should not be used during pregnancy. The Center for Disease Control advises against the use of podophyllin in the urethra, on the cervix, and in the anorectal region. If the wart has not regressed after 4 weekly applications, alternative regimens such as cryotherapy, electrosurgery, or surgical removal are advised.

Recent advances in laser therapy make it an excellent treatment for condyloma. Calkins et al have reported recurrence rates as low as 9% after laser treatments.[55] Advantages of the laser over conventional therapeutic alternatives include its applicability to extensive lesions where podophyllin would be ineffective and even toxic if used in large amounts. Additionally, blood loss is insignificant compared to surgical removal and most patients report only minor pain during outpatient vaporization. A protocol for managing condyloma acuminata is presented in Table 17-2.

Table 17-2. Schemata for Management of Condyloma Acuminata with Outpatient Laser Therapy.



[a]This assumes (1) no lesions on vagina and cervix; (2) if there are white lesions on cervix, they should be removed at the same time; (3) careful anal evaluation and treatment as indicated; and (4) individualized care for pregnant patients.

[b]If condyloma recurs, patient education should include discussion of necessity of having sexual partner's urethra examined, particularly in absence of lesions on sexual partner's external genitals.

Trichomonas

Trichomonas vaginalis is a frequent cause of sexually transmitted vaginitis. Reports indi-

cate that the organism may be identified in 3–15% of asymptomatic females who go to gynecology clinics and in 20–50% of those at sexually transmitted disease clinics.[56] Trichomoniasis frequently is seen in association with gonorrhea, with investigators reporting coexistent rates of approximately 40%.[57] It generally is accepted that the protozoan is sexually transmitted; however, trichomoniasis has been found in patients who have not had intercourse.[58]

Patients with symptomatic infection usually will complain of a malodorous, uncomfortable discharge. Frequently there will be complaints of dysuria, but as many as 50% are asymptomatic.[57] The cervix may exhibit erythema or the classical strawberry appearance. The discharge will be copious, ranging in color from green to white. It typically has a pH 4.5, a week amine odor, and a large number of trichomonads and white blood cells on the saline wet microscopic preparation.[59] Although some investigators advise culture and isolation of the organism, the necessity to maintain fresh culture media makes this practical only in high-risk sexually transmitted disease clinic populations. Frequently, Pap tests will reveal organisms consistent with trichomonads; however, this should be confirmed by wet preparation because of high false-positive rates.[60]

Recommended therapy (adult weight) is 2.0 g of metronidazole in a single oral dose.[11] An alternative is metronidazole, 250 mg three times a day for 7 days. Asymptomatic women with trichomonas infection also should be treated with the same recommended dose of metronidazole, as should all sex partners. All patients should be evaluated for coexistent sexually transmitted diseases. Infants older than 4 weeks who have symptomatic trichomoniasis or urogenital colonization can be treated with metronidazole, 10–30 mg/kg daily for 5 to 8 days. Metronidazole is contraindicated in the first trimester of pregnancy and should be avoided throughout pregnancy. An alternative therapy is clotrimazole, 100 mg intravaginally at bedtime for 7 days. Lactating women may be treated with metronidazole, 2.0 g orally in a single dose, provided breast-feeding is interrupted for 24 hours after therapy.

Premenarchal Vulvovaginitis

While this chapter has dealt with specific infections of sexually transmittted diseases, there is a category of patients that should be considered separately. The premenarchal female with vulvovaginitis often presents a diagnostic dilemma. Understanding and sensitivity to the child are crucial during any examination; psychologic scarring can easily result from hasty genital inspection. Although vulvovaginitis in this age group does not constitute a large portion of a gynecologic practice, it does represent 85–90% of the genital disorders seen in premenarchal females. A significant number of these patients will have sexually transmitted diseases. Paradise et al[61] evaluated 54 premenarchal females with signs and/or symptoms of vulvovaginitis and the mean age of this group was only 5.8 years. Bacterial or monilial infection was found in 26 patients who had vaginal discharge, and in no one without discharge. Four patients had *N. gonorrhoeae* isolated. The study concluded that patients this age with vaginal discharge are likely to have specific infections, and cultures, especially for *Neisseria*, should be obtained. Alausa and Osoba reported on 42 children between the ages of 1 and 12 with gonococcal genital infections.[62] Presumed methods of spread included contaminated fomites (bedclothing, underclothing, towels) and sexual intercourse. Additional causes for vaginal discharge include vaginal fistulae, ectopic ureters, shigella, candida, pinworms, and foreign bodies. Nonspecific vulvovaginitis may present as a yellowish discharge that is usually self-limiting and not associated with vulvar irritation.

Diagnosis requires an examination and culture of the discharge. The "frog leg" or knee-chest position in association with Valsalva maneuvers will increase visibility of the lower vagina. Rarely is an examination under anesthesia or vaginoscopy necessary. If foreign bodies are found that cannot be removed or dislodged with gentle, warm saline irrigation, or if developmental or traumatic abnormalities are suspected, an examination under anesthesia should be considered. Therapy for the specific causes should be based on microscopic and microbiologic findings. Therapy

for *N. gonorrhoeae* has been previously discussed. Monolial infections are best treated with topical candicidal creams. For the child with "sand box" vaginitis caused by sand between the folds of the labia and vagina, snug underwear and cleansing of the vulva will suffice. Irritations as a result of aerosol deodorant sprays, bubble baths, laundry detergents, and nylon panties can be resolved by eliminating the offending agent. Nonspecific vaginal discharge may occur until menarche. The use of cotton underwear with frequent changes is the only therapy recommended. Talcum powder or cornstarch may be used to decrease vulvar moisture and alleviate irritation. If the irritation becomes chronic, daily warm sitz baths without medication are helpful. Perineal cleansing is important in preventing vulvar contamination with fecal material (daily for 7 to 10 days). Short-term estrogen creams may be necessary to thicken the layers of the vaginal mucosa to provide resistance to infection, but the prolonged use of estrogen creams may cause pseudoprecocious puberty in children.

Finally, the role of the physician in reporting suspected child abuse must be emphasized. If *N. gonorrhoeae* is isolated or if physical examination indicates the possibility of sexual abuse, the physician must notify social services and legal authorities. The physician's reluctance to become involved may be understandable; his failure to do so is inexcusable.

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Contraception 18

Donald E. Greydanus

Adolescence is a complex time during which the child passes through a series of psychologic and physiologic stages on the way to becoming an autonomous adult. A major part of the process is the establishment of sexuality, whereby the child gradually learns to become sexual.[1] Studies have shown that millions of America's 40 million teenagers are sexually active, resulting in 1.3 million pregnancies each year as well as millions of cases of sexually transmitted diseases.[2]

For the past decade there has been a trend toward earlier and more frequent intercourse. In the early 1970s, Sorensen[3] surveyed 400 American teenagers and found that 44% of males and 30% of females 13 to 15 years old were sexually active; these figures rose to 72% of males and 57% of females in those 16 to 19. Further studies have agreed with this general observation, the most comprehensive of which are several reports by Zelnik and Kantner.[4,5] In 1972, their study reported sexual activity for unmarried females at the following rates: 14% at 15, 21% at 16, 27% at 17, 37% at 18, and 46% at 19.[1] A 1976 report noted an increase: 18% at 15, 25% at 16, 41% at 17, 49% at 18, and 55% at 19.[4] Rates for males generally were higher, up to 69% of single 19- to 21-year-olds. An increase in the number of sex partners also has been observed: 31% of girls have had two or three partners, and 10% have had more than five.

Although it is clear that coital activity among teenagers is on the rise, this has not increased the average teenager's knowledge about sexuality. Although most teenage pregnancies are unwanted, many teenagers either forego contraceptives altogether or use them haphazardly. The use of contraceptives by teenagers is a complex issue and involves motivation, information, and adequate access.[2,6] Some adolescents actively try to become pregnant, whether as a desperate attempt to "better" their own lives or to manipulate their parents or sex partners. Moreover, young teenagers often do not equate coitus with eventual pregnancy, whereas others feel they are somehow protected from the consequences of unprotected sex.

Many reasons are given by pregnant girls who did not want to become pregnant—yet did not use effective contraception. A study of pregnant teenagers by Zelnik and Kantner found that more than 50% believed they could not become pregnant, 25% thought it was a safe time of the month to have intercourse, and 21% did not anticipate having intercourse.[5] Other reasons cited for not using a contraceptive include a feeling that they were too young to become pregnant, that contraception was dangerous or wrong, that coitus was too infrequent to result in pregnancy, and/or a lack of knowledge about contraceptive techniques. Teenage boys also are often uninformed about contraception. To compound the problem, they often relegate the responsibility of contraception to the girl or object to the use of any birth control. To make matters worse, many youth become pregnant soon after their first sexual experience (sexarche), often waiting several months to seek contraception.

This chapter concentrates on *methods* of contraception that are available to teenagers. It is based on the premise that there are many youth who are or who can be motivated to effectively use contraceptives and avoid unwanted pregnancy. The issues of adolescent sexuality, sex education, and psychosocial motivations behind effective contraception are discussed in Chapter 1. Any health care professional who deals with sexually active teenagers must be knowledgeable about which contraceptives are acceptable and unacceptable for young people.

The ideal contraceptive is the method that is 100% effective in preventing pregnancy, has no side effects, can be used easily, and produces reversible sterility. Unfortunately, no contraceptive is perfect for all teenagers. When the health care professional encounters a sexually active youth who wishes contraception, the clinician must help the *patient* decide the method that is best for her.

Table 18-1 outlines the contraceptive methods reviewed in this chapter. These methods have evolved over the centuries, although the most significant developments have occurred in the past 30 years. Table 18-2 reviews this progress from a historical perspective. Of major importance is that oral contraceptives remain the most popular method for girls who use contraception.[7,8] In a 1973 study of married women ages 15 to 24, 44.9% used the pill compared with the intrauterine device (IUD) (7.2%), the condom (5.7%), vaginal foam (2.7%), rhythm (1.3%), the diaphragm (1.1%), withdrawal (0.8%), douche (0.2%), and other methods (5.1%).[9] Other studies and reviews agree that oral contraception is the most popular contraceptive among teenagers who use a specific medical method. It also is important to realize that all these methods are far safer for teenagers than pregnancy and childbirth.[10,11] Proper contraceptive assignment also will reduce morbidity and mortality, as will frequent medical follow-up.

Table 18-1. Contraceptive Methods for Adolescents.

- A. Combined birth control pill (estrogen and progestin)
- B. Minipill (progestin-only pill)
- C. Barrier methods
  1. Condom
  2. Diaphragm
  3. Cervical cap
  4. Vaginal contraceptives (creams, foams, jellies, powders, pastes, suppositories, tablets, other)
  5. Vaginal sponge
- D. Intrauterine contraceptive devices
- E. Postcoital contraceptives
  1. Diethylstilbestrol
  2. Other estrogens (ethinyl estradiol or conjugated estrogens)
  3. Minipill
  4. Estrogen and progestin combination
  5. Intrauterine contraceptive devices
- F. Injectable contraceptives
  1. Medroxyprogesterone acetate
  2. Norethindrone enanthate
  3. Others
- G. Rhythm methods
  1. Basal body temperature
  2. Calendar method
  3. Fertility awareness or Billing's Ovulation Method
  4. Others
  5. Combinations
- H. Lactation
- I. Sterilization
- J. Abortion
- K. Miscellaneous methods
  1. Douche
  2. Coitus interruptus ("strategic withdrawal")
  3. Masturbation
  4. Other noncoital sexual activity (or abstinence)

Oral Contraception: Overview

There are more than 145 brands of oral contraceptives that consist of a combination of synthetic estrogen and synthetic progestogen. The estrogens in oral contraceptives sold in the United States are ethinyl estradiol or mestranol, while the five progestins available are norgestrel, ethynodiol diacetate, norethindrone acetate, norethindrone, and norethynodrel (Figure 18-1).[12] Other oral contraceptives are available in various parts of the world (Table 18-3). The five progestins used here usually are designated as having various endocrine qualities, whether estrogenic, androgenic, anabolic, or antiestrogenic. (Table 18-4).[13,14] These classic divisions are controversial because progestin potencies are compared by using various animal models, by their effect on causing delayed menses or withdrawal bleeding, and on their potency in inducing glycogen vacuoles in human endo-

Table 18-2. Historical Outline of Development in Contraception.

Date	Event
1900 B.C.	Egypt: Known use of prolonged lactation and barrier methods (placing various substances in the vagina: wine, garlic, gums, honey, and even crocodile dung).
1500 B.C.	Genesis 38:8,9 mentions and condemns coitus interruptus. Leviticus XV discusses douching (probably for hygienic reasons) and various public health measures to prevent or deal with probable sexually transmitted diseases.
1900 B.C.	Egypt: Known use of prolonged lactation and contraceptive technique.
1500 B.C.	Genesis 38:8,9 mentions and condemns with a pessary, utilizing various acidic ingredients.
1564	Gabriel Fallopius recommends a damp linen cloth as a protection from syphilis.
Late 1700s	Condom is advocated in London and elsewhere as a venereal disease prophylactic.
1838	Wilde advocates the use of a rubber cervical cap.
1850	Charles Knowlton recommends contraception with a postcoital douche using alum and other ingredients.
1880	Lungren performs a tubal sterilization and initiates the modern era of sterilization as a means of permanent contraception.
1882	Wilhelm Mensinga, a pseudonym for Dr. Hasse, develops an early prototype of a diaphragm.
1897	Beard postulates that the ovarian corpus luteum of pregnancy is responsible for inhibition of ovulation.
1909	Richter uses a silkworm gut-type of intrauterine device.
1920s	Margaret Sanger introduces the diaphragm to the United States.
1929	Graefenberg advocates the use of an intrauterine device as a safe and effective contraceptive method.
1930	Mayer demonstrates in vitro the possible contraceptive effect of estrogens on the ovary.
1938	Baker introduces a vaginal contraceptive.
1949	Eastman and Seidelo discuss the effectiveness of a vaginal suppository or jelly as sole contraceptive methods.
1956	Pincus advocates development of oral contraceptives, due to the production of synthetic progesterone.
1956	The development of surface active agents (nonoxynol-9) in vaginal contraceptives.
1959	Oppenheimer advocates the use of the Graefenberg ring.
1960	Enovid, the first oral contraceptive, is commercially available. Modern era of effective oral contraception now is underway.
1961	The first commercially available aerosol vaginal contraceptive is introduced.
1963	Siegel discusses the use of periodic progesterone injections.
Late 1960s	Progesterone-only pills ("minipill") developed, with the hope of providing effective contraception without combined-pill side effects.
1972	Male contraceptive pill is developed in China.
1973	Contraceptive film ("C-film") commercially available.
1983	Vaginal sponge commercially available.
1980s	Possible development of other medical contraceptive methods, including various release vehicles for progesterone, contraceptive vaccines (male or female), male contraceptive pills, postcoital contraceptive-type pills for more frequent use, prostaglandin tampons (Table 18-3).

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Table 18-3. Miscellaneous Contraceptive Estrogens and Progestins.

A. Estrogens
- Deposiston (ethinyl estradiol-3-isopropyl sulphonate)
- Quinestrol (ethinyl estradiol-3-cyclopentyl ether)

B. Progestagens
- Quingestanol acetate (3-cyclopentyl-norethisterone acetate)
- Levonorgestrel
- Desogestrel (3-deoxy-11-methylene-levonorgestrel)
- Norgestrienone (10,11-didehydro-orethisterone)
- Norgesterone (vinyl-norethynodrel)
- Megestrol acetate
- Cyproterone acetate
- Superlutin
- Chlormadinone acetate
- Medroxyprogesterone acetate
- Lynestrenol (3-deoxy-norethisterone)

From ref. 94.

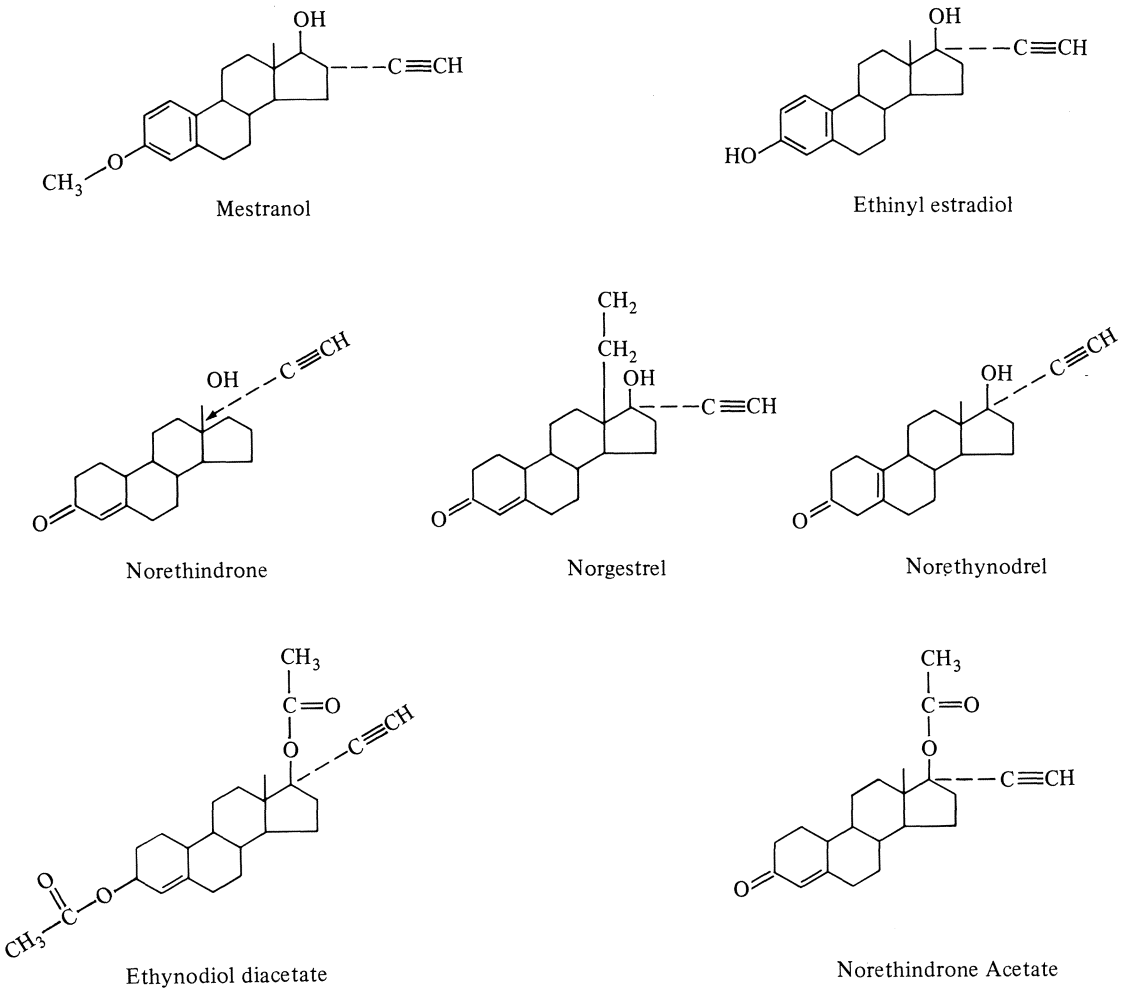

Figure 18-1. Formulas of estrogen and progestins in common contraceptives.[17,21,94]

Table 18-4. Relative Biologic or Endocrine Effects of Progestagens.

Progestagen	Estrogenic	Antiestrogenic	Anabolic (Progestational)	Androgenic
1. Norgestrel	0	+4	0-+2	+2
2. Ethynodiol diacetate	+1-+2	+2	+1	+1
3. Norethindrone acetate	0-+1	+1	+1-+2	+1
4. Norethindrone	0-+1	+1-+2	+1	+2
5. Norethynodrel	+2	0	0-+1	0

metrium.[15] However, studies often differ when comparisons are made.[16] Moreover, the difference between estrogens depends on whether animal or human models are used. Ethinyl estradiol is more potent than mestranol in rats, but studies on human endometrial biopsies indicate they are equally potent, although mestranol actually is converted to ethinyl estradiol by splitting off a methyl ether group.

It generally is established that the combined oral contraceptive is one of the most effective methods available.[17-19] When taken regularly, pregnancy rates are well under one per 100 woman-years of use. Both estrogen and progestin can inhibit ovulation, but this combination produces extremely reliable ovulation prevention by inhibiting follicle stimulating hormone (FSH) and luteinizing hormone (LH).[20] In addition, there is endometrial atrophy that has the potential to prevent implantation and a thickening of cervical mucus to reduce sperm penetration.[21] Although there is a wide variety of test results affected by the pill (Table 18-5),[22-25] usually these laboratory alterations are of limited clinical consequence for a healthy teenager.

Traditionally, birth control pill side effects are listed as partially estrogen-related or progestogen-related (Table 18-6).[26,27] Thus, various symptoms have been controlled by switching pill brands to change the estrogen or progestogen ratio. However, it cannot be accurately predicted what side effects are *solely* related to either estrogen or progestogen. Moreover, the types of oral contraceptives available are limited because it is recommended that to reduce the risk of thromboembolic disease only those brands with no more than 50 μg of estrogen be used. Clinicians often find teenagers very impatient with side effects and not always tolerant of frequent brand switching. Table 18-7 lists problems that often are of concern to teenagers along with suggested management options (see Low-Estrogen Oral Contraceptives, below).

Rather than emphasizing estrogen- or progestogen-related side effects or all the possible laboratory alterations, it is more helpful to concentrate on what this means to the teenager who wants to use oral contraceptives. Thus, it is necessary to note the myriad absolute and relative *contraindications* of oral contraceptive use (Table 18-8).[2] The American College of Obstetricians and Gynecologists recommends the following six conditions as absolute contraindications for the pill: history of thromboembolism or thrombotic disease, active acute or chronic liver disease, undiag-

Table 18-5. Laboratory Tests Affected by Oral Contraceptives.

A. Values which are increased (serum values, unless otherwise stated)
   1. Erythrocyte sedimentation rate (sometimes the hematocrit, white blood cell count, and platelets)
   2. Serum iron and iron-binding capacity
   3. Sulfobromophthalein and bilirubin
   4. Serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and serum gamma-glutamyl transpeptidase
   5. Alkaline phosphatase
   6. Clotting factors I, II, VII, VIII, IX, X, and XII; also increased antiplasmins and antiactivators of fibrinolysis
   7. Triglycerides, phospholipids, and low density lipoproteins (sometimes the serum cholesterol)
   8. Serum copper and ceruloplasmin
   9. Increase in various binding proteins (transferrin, transcortin, thyroxine-binding globulin)
   10. Renin, angiotensin, angiotensinogen, and aldosterone
   11. Insulin, growth hormone, and blood glucose
   12. C-reactive protein
   13. Globulins (alpha-1 and alpha-2)
   14. Alpha-1-antitrypsin
   15. Total estrogens (urine)
   16. Coproporphyrin (feces and urine) and porphobilinogen (urine)
   17. Vitamin A
   18. Xanthuric acid (urine)
   19. Positive antinuclear antibody test and LE preparation
   20. GAP (globulines anormalement precipitables; Beaumont protein)

B. Values which are decreased
   1. Antithrombin III
   2. LH and FSH
   3. Pregnanediol and 17-ketosteroids
   4. Folate and vitamin B_{12}
   5. Glucose tolerance
   6. Ascorbic acid
   7. Zinc and magnesium
   8. T-3 resin uptake
   9. Fibrinolytic activity
   10. Haptoglobulin
   11. Cholinesterase
   12. High density lipoproteins

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Table 18-6. Oral Contraceptive Side Effects.

A. Estrogen-induced
   1. Nausea and/or emesis
   2. Dysmenorrhea and/or premenstrual tension (with or without edema)
   3. Elevated blood pressure
   4. Vascular headaches
   5. Cervical erosion and/or polyposis
   6. Increased mucoid vaginal discharge
   7. Tender breasts or fibrocystic breast disease
   8. Fluid retention (weight gain)

B. Progestin-induced
   1. Decreased menses
   2. Reduced vaginal secretion
   3. Breast regression
   4. Weight gain (with increased appetite)
   5. Fatigue
   6. Depression
   7. Acne
   8. Hirsutism
   9. Reduced libido
   10. Leg cramps
   11. Alopecia
   12. Others

Table 18-7. Management of Some Oral Contraceptive-Related Problems.

Problem	Management
Weight gain or edema	Use 30- or 35-μg estrogen pill (e.g., Norinyl 1 + 50 or Ortho-Novum 1/35).
Acne	Usually controlled with antiacne medications: benzoyl peroxide, tretinoin, and antibiotics (topical or systemic). For a youth with acne or hirsutism, try a pill with low androgenic effects: Demulen Norinyl 1 + 50, or Ortho-Novum 1/50.
Acute monilial vaginitis	Usually controlled with antifungal agents given intravaginally: miconazole nitrate 2% (Monistat 7 vaginal cream), h.s. for 7 nights; clotrimazole vaginal cream or vaginal tablets (Gyne-Lotrimin), h.s. for 7 nights; nystatin vaginal tablets (Mycostatin), twice daily for 14 days.
Chronic monilial vaginitis	Treat for an entire menstrual cycle; evaluate for other factors (broad spectrum antibiotic use, endocrinopathies, infected male genital tract, others); male partner can use a condom; use of oral nystatin to reduce gastrointestinal reservoir; many others.
Breakthrough bleeding (intermenstrual spotting)	Usually resolves without treatment after 2 to 3 subsequent cycles. Otherwise use a 50-μg pill. Finally, give 10–20 μg ethinyl estradiol for 7–10 days. Be sure the patient is taking the pill *every day*.
Possible pregnancy	Stop the pill immediately since some consider it to be a mild teratogen. See text for details.
Other side effects (see text)	Monitor any side effects very carefully; patient must allow frequent evaluation as determined by the physician; Some problems (e.g., melasma) need immediate cessation of the pill.

nosed uterine bleeding, pregnancy, breast cancer, and estrogen-dependent neoplasia. Fortunately, breast cancer and other estrogen-dependent neoplasia are rare in teenagers. However, teenagers evaluated for oral contraceptives should be carefully screened for these conditions. Aside from these absolute contraindications, there are many problems for which the pill puts the adolescent at an increased morbidity risk, but where the risk is often less than that associated with pregnancy. Relative contraindications are listed in Table 18-9.

A major requirement for successful oral contraceptive use is the ability of the youth to take the pill every day. Those who find it difficult to comply should find another method of contraception. Table 18-9 offers a proposed approach for the teenager who requests oral contraceptives. In general, a pill with 30–50 μg estrogen and 0.15–1.5 mg progestogen is recommended (see below).[25] A careful evaluation is recommended and if any relative contraindications to pill use are found, it is the job of the clinician to determine if the girl remains an acceptable candidate for the pill.[26] The presence of relative contraindications does not necessarily mean she cannot take the pill. The risk of pregnancy and its related problems may be enough to make the pill the best choice, especially if she refuses or it not clinically recommended for other contraceptive methods. If an absolute contraindication is noted, under no circumstances should she be given the pill.

Frequently, a youth can use the pill for a brief time until she is psychologically mature enough to accept other contraception such as a barrier method. It is necessary in these cases to view the use of oral contraceptives as a

Table 18-8. Contraindications to Oral Contraception.

- Absolute Contraindications
  - Pregnancy
  - Undiagnosed genital bleeding
  - Estrogen-dependent cancer
  - Active liver disease (acute or chronic)
  - History of thromboembolic disease
  - Severe migraine headaches (especially with prolonged auras)
  - Severe hypertension
  - Hyperlipidemia
  - Cyanotic heart disease
  - Inability to take the pill each day for a prolonged length of time
  - Inability to return for follow-up visits to the physician as needed
- Relative Contraindications
  - Diabetes mellitus
  - Epilepsy
  - Sickle cell disease
  - Collagen vascular disease
  - Uterine leiomyomata
  - Lactation
  - Oligomenorrhea
  - Depression
  - Estrogen-related dermatologic disorders (melasma, erythema nodosum)
  - Gallbladder disease
  - Inflammatory bowel disease
  - Hypothalamic-pituitary dysfunction
  - Chorea
  - Porphyria
  - Coagulation defects
  - Renal disease
  - Pulmonary disease
  - Cardiac disease
  - Retinal disorders
  - Severe, chronic monilial vaginitis
  - Various drug interactions (Table 18-11)
  - Severe chest or abdominal pain of unknown etiology
  - Others

Table 18-9. Suggested Plan to Evaluate Adolescents for Birth Control Pills.

A. Gathering of appropriate historical data.
   1. Does the patient need and want contraception?
   2. Does she understand what methods of contraception are available?
   3. What is her menstrual history?
      a. Age of menarche.
      b. Are menstrual periods regular? For at least one year?
      c. Date of last menstrual period.
      d. Are there any previous pregnancies or abortions?
      e. Does she need or wish additional sexuality counseling?
   4. Will she accept the use of a barrier method (diaphragm with contraceptive jelly or condom with contraceptive foam)?
   5. After discussion of the various options, has she chosen the birth control pill (BCP)? What concerns does she have about BCPs?
   6. Can she take these pills on a daily basis?
   7. Are there absolute contraindications to BCP use (see text)?
   8. Are there relative contraindications (see text)? Discuss the risks and benefits with the patient and arrive at a mutual decision. Usually BCPs should be avoided with:
      a. Hypertension.
      b. Severe migraine headaches.
      c. Hyperlipidemia.
      d. Sickle cell disease.
      e. Uncontrolled epilepsy.
      f. Poorly controlled diabetes mellitus.
      g. Significant chest pain of unknown etiology.
      h. Optic nerve or retinal disease.
      i. Clotting abnormalities.
      j. Melasma or "mask of pregnancy."
      k. Chronic illness is not necessarily a contraindication for BCP use. Evaluate each patient carefully.
   9. Is there a history of acne vulgaris or monilial vaginitis? These may develop or worsen with BCP use but usually can be effectively treated without the need to discontinue BCPs (Table 18-7).
   10. Does she wear contact lenses? Development of edema may prevent their use.

B. Physical examination. A complete examination is necessary, with emphasis on the following:
   1. Tanner staging for pubertal assessment (should be stage IV or V).
   2. Blood pressure.
   3. Sclera (i.e., jaundice?), fundi, vision.
   4. Thyroid examination.
   5. Breast examination.
   6. Evaluation of cardiovascular system.
   7. Evaluation of the liver (size and tenderness). Stigmata of hepatitis or chronic liver disease?
   8. Skin evaluation: acne vulgaris, melasma, xanthomas.
   9. Complete pelvic examination, including a Pap test and cervical culture for *N. gonorrhoeae* and possibly

Table 18-9. *(continued)*

C. trachomatis. Evaluate for other sexually transmitted diseases and monilial vaginitis.

C. Laboratory data.
   1. Urinalysis, including a microscopic examination.
   2. Liver function tests if the liver status is in doubt (i.e., recent history of viral hepatitis).
   3. Screen for *N. gonorrhoeae* and *C. trachomatis* (cervical culture).
   4. Pap test.
   5. Triglyceride and cholesterol screen, if there is a history suggestive of hyperlipidemia (i.e., close relatives dying under the age of 50 from myocardial infarction).

D. Recommendations (after the evaluation, as outlined above).
   1. If having regular coitus, does not want a barrier method(s), understands and chooses the BCP, then consider this method.
   2. Avoid the BCP if any absolute contraindications are noted (see text).
   3. Discuss the situation if relative contraindications are noted (see text).
   4. Inform her of possible side effects such as acne, monilial vaginitis, weight gain, and edema.
   5. Prescribe a 30-μg tablet using the 28-day packets, starting on day 5 of the menstrual period. If breakthrough bleeding develops (i.e., intermenstrual spotting) and continues for one to three further cycles, use a 50-μg tablet. If symptoms suggestive of excess estrogen develop, lower the estrogen level (50 μg to 30 μg). In general, use a pill with 0.15–1.5 mg progestin.
   6. Use other contraceptive methods for the first 7 days of the first packet. If one pill is missed, take it as soon as it is remembered and take the next one in proper sequence. If two or more pills are forgotten, then the contraceptive potential is reduced and the patient should use another contraceptive method. A re-evaluation of her contraceptive alternatives should be done.
   7. The patient should refrain from smoking (*relative* contraindication).
   8. The BCP is not recommended for a prolonged time (i.e., more than 4 to 6 years). There are no data on optimal usage durations.
   9. If the BCP is contraindicated, consider the minipill (see text).
   10. The patient should stop the BCP if pregnancy is suspected and contact her physician.
   11. She is encouraged to contact her physician or health agency if questions, worries, or difficulties arise.
   12. If she wishes to stop taking the BCP, evaluation for an alternative method is necessary.
   13. Frequent follow-ups for the *teenager* on BCP: the first postprescription visit in 6 to 8 weeks, then every 3 to 6 months, with *N. gonorrhoeae* (plus *C. trachomatis*) culture every 6 months and annual Pap tests. Discuss the development of any symptoms related to BCP use.
   14. The approach to each patient must be individualized, based on a basic fund of information about contraceptive methods and facility for examining the female adolescent.

Table 18-10. Benefits of Oral Contraception.

1. Reversible pregnancy prevention
2. Menstrual regulation
3. Improvement in menstrually induced anemia
4. Improvement in dysmenorrhea
5. Protection from pelvic inflammatory disease
6. Less benign breast disease
7. Less ovarian cyst formation
8. Improved protection from ectopic pregnancy
9. Cancer protection (lower incidence of endometrial, ovarian, and breast cancer) (see text)
10. Improved protection from rheumatoid arthritis
11. Others

transient pregnancy alternative. Thus, for example, the pill may be recommended for youth with certain chronic illness, mild migraine headaches, irregular menstruation, or cigarette addiction. Alternative methods later can be offered. It is important for the clinician to inform the teenage patient what the risks may be and then help her decide. Teenagers frequently have inaccurate information about the pill; thus, health care professionals must clear up any misconceptions.[28] The benefits of the pill also should be discussed (Table 18-10).

Oral Contraceptives: Pill-Influenced Conditions

Cardiovascular-Cardiopulmonary Complications

Thromboembolism

Oral contraceptives were linked to an increase in thromboembolism shortly after they appeared on the market in 1960. Women on combined oral contraceptives do indeed have an increased risk of vascular thromboses,

thrombophlebitis, and pulmonary emboli.[29] The estrogen component of oral contraceptives usually is implicated. However, there are conflicts over what is the actual risk. For example, Porter et al[30] noted a correlation between oral contraceptives and venous thromboembolism but found no evidence of a link between birth control pills and stroke. However, various British studies have correlated the pill with increased thrombotic stroke and myocardial infarctions.[31] The Walnut Creek study observed a correlation with subarachnoid hemorrhage, but found no link with either thrombotic stroke or myocardial infarction.[32] A recent review by Mammen notes that coagulation factor changes induced by the pill generally are of minimal clinical significance.[33] Most experts agree that the increased risk of thromboembolic phenomena is mainly to women over 35, especially if they are regular cigarette smokers, and that the use of low-estrogen pills (30–50 μg) significantly reduces this risk.[34] What also is clear is that teenagers on low-estrogen pills are at minimal risk and that thromboembolic complications are rare in this age group.[19,25,35] The mortality rate for females 15 to 19 is 1.2 deaths per 100,000 pill users who do not smoke and 1.4 for smokers. The mortality rate from pregnancy and childbirth, however, is 11.1 per 100,000 live births.[2]

Teenagers who are examined to see if they are candidates for the pill should be screened for factors that increase the risk of thromboembolic phenomena. Smoking more than 10 cigarettes per day does increase the risk but only slightly in teenagers, and thus is a relative contraindication. Also, teenagers who take the pill have an increased risk of postoperative thromboembolic phenomena. Therefore, they should stop the pill 6 to 8 weeks prior to elective surgery. If the pill is not discontinued, heparin should be given postoperatively. If significant risks are noted for thromboembolism, alternative methods of contraception can be recommended such as medroxyprogesterone acetate, the minipill, or barrier methods.

Cardiopulmonary Disorders

The increased risk of coronary artery thrombosis and myocardial infarction associated with the pill occurs in women well beyond adolescence.[36] Ventricular and spirometric studies on healthy women taking oral contraceptives have found no deterioration in cardiopulmonary functioning. However, significant deterioration in cardiopulmonary status has been observed in pill users who have congenital cardiac defects and rheumatic heart disease. Thus, the pill should be avoided in youths who have rheumatic heart disease (valve defects such as aortic or pulmonary stenosis), cyanotic heart disease, pulmonary hypertension, or bacterial endocarditis. Girls with nonvalvular rheumatic heart disease, small left-to-right shunts, or mild asthma without chronic pulmonary sequelae need not necessarily avoid the pill. However, asthmatics who are given the pill may need a change in their normal theophylline dose because the pill delays elimination of this antiasthmatic drug.

A mild increase in blood pressure is noted in 5–18% of pill users.[9] It usually is reversible and involves a rise of 5–8 mmHg systolic and 1–3 mmHg diastolic pressure. Both estrogen and progestin are implicated.[15,37] The cause has been related to activation of the renin-angiotensin-aldosterone system and hypervolemia as a result of sodium and water retention. There also may be increased catecholamine and/or adrenergic activation. Of specific concern are the few persons who unpredictably develop severe, malignant hypertension, with or without irreversible renal damage or failure. Recent studies have related severe hypertension in oral contraceptive users to a decreased prostacyclin.[38]

Teenagers should be screened and monitored for elevated blood pressure.[19] While mild hypertension is not necessarily a contraindication to the pill, other causes should be carefully sought, including essential hypertension, renal disorders, cardiovascular disorders, central nervous system disorders, and drug-induced or anxiety-induced hypertension. If the evaluation is negative and the blood pressure normalizes after discontinuing the pill, oral contraceptives can be implicated. Those with increased blood pressure should be monitored carefully and the pill discontinued if the diastolic pressure exceeds 102 to 104 mmHg and/or if hypertensive complications develop. Careful observation also is

important if there is a history of hypertension during pregnancy or a significant family history of hypertension and cardiac disease. A lower estrogen pill may have less effect on blood pressure, while there may be essentially no change with the minipill.[39,40]

Oligomenorrhea

A frequent recommendation is that a girl not be given the pill until she has regularly menstruated for 1 to 2 years.[41] However, many teenagers have irregular menses for up to 3 years after menarche and still may be capable of conceiving. Therefore, irregular menstruation should be a *relative contraindication* to pill use. There is no evidence that the pill oversuppresses the hypothalamic-pituitary-ovarian axis and that teenagers with irregular menses will develop postpill amenorrhea.[25,42]

The phenomenon of postpill amenorrhea is controversial. Although 0.7–2.2% of women note a 6-month or more absence of menstruation after discontinuing the pill, it has not been proven that the pill is a direct cause.[9,43,44] A careful evaluation is necessary after 6 months of amenorrhea and includes looking for a prolactin-producing pituitary adenoma.[17] Although the pill can raise prolactin levels, there is no evidence that oral contraceptives cause pituitary adenomas.[45,46]

Thus, when faced with a teenager who has oligomenorrhea or other menstrual irregularity, the clinician should do a thorough evaluation.[21] Causes may include physiologic immaturity, polycystic ovary syndrome, weight loss, and stress. In general, girls with irregular menses—especially if they have never been regular—should be given other contraceptive methods. However, if they are at high risk for pregnancy and will not use another method, the pill may be recommended. There is no evidence that the pill will oversuppress the pubertal axis, limit growth, or lead to further menstrual irregularity.[19]

Many adolescent female athletes who exercise vigorously and have a reduced body fat–body weight ratio develop irregular menses and even primary or secondary amenorrhea.[47] (see Chapter 24). Females with a ratio below 17% may have delayed menarche, and those whose ratio is below 22% may develop secondary amenorrhea or oligomenorrhea. The cause may be a reduction in peripheral fat stores, which causes less estrogen-induced stimulation of the hypothalamic-pituitary-gonadal axis. The long-range effect on athletic teenagers with irregular or absent menses is unclear. The clinician should caution the sexually active youth in this situation that irregular or absent menses does not mean she cannot get pregnant. Although recent studies indicate that many serious athletic adult women often choose barrier methods, the pill is used by many young athletes.[48]

Finally, it should be understood that it is common for *breakthrough bleeding* to occur in the first few months after starting the pill—especially if a low-estrogen pill is used.[21,49] This usually is mild and resolves over the next few cycles. A result of estrogen deficiency, breakthrough bleeding sometimes necessitates a switch from a 30- or 35-μg estrogen pill to one with 50 μg. Doubling up on the pills is not recommended. Sometimes supplemental estrogen (10–20 μg/day of ethinyl estradiol) is needed for 7–10 days. Breakthrough bleeding that occurs several months after pill initiation usually is due to a progestogen deficiency and often responds to a pill with more progestogen effect (Norlestrin 2.5/50, Lo/Ovral, Nordette, Ovral, or Loestrin 1.5/30). A careful

Table 18-11. Drugs Interfering with Oral Contraceptives.

A.	Antibiotics
	1. Rifampin
	2. Chloramphenicol
	3. Ampicillin
	4. Penicillin
	5. Sulfonamides
	6. Nitrofurantoin
	7. Neomycin
	8. Isoniazid
B.	Anticonvulsants
	1. Phenytoin
	2. Primidone
	3. Phenobarbital
	4. Ethosuximide
C.	Others
	1. Chlordiazepoxide
	2. Phenylbutazone
	3. Meprobamate
	4. Cyclophosphamide
	5. Chlorpromazine
	6. Phenacetin

Source: refs. 50–52.

search for underlying causes is important, and the clinician should be assured that the youth is indeed taking the pills.

An absence of withdrawal bleeding also can occur even when the pill is taken as directed. For example, drug interactions may render the pill less effective (Table 18-11).[21,26,27,50-52] The metabolism of various medications in the liver may increase microsomal enzymes, the results of which are increased pill metabolism and decreased pill contraceptive effect. Moreover, gastroenteritis may limit pill absorption for a time, leading to a pregnancy. If, however, a youth on the pill does not have withdrawal bleeding, yet is not pregnant, reassurance can be given. Switching to a brand with higher estrogen activity may be all that is necessary to cause a withdrawal bleed. Occasionally, exogenous estrogen is necessary.

Diabetes Mellitus

Oral contraceptives cause a reduced glucose tolerance, although the pill does not cause diabetes per se in a normal person.[53,54] Increased blood glucose is due to mechanisms that include liver function changes, elevated cortisol and growth hormone levels, alteration of gastrointestinal factors, and changes in peripheral glucose utilization. Teenagers with subclinical or gestational diabetes can develop overt diabetes when given the pill. Studies have implicated both the pill's estrogen and progestin components.

Most clinicians regard diabetes as a *strong relative contraindication* to oral contraceptives because there is concern over the worsening of diabetic complications.[55] The pill can induce increased insulin demands, increased triglycerides as well as total cholesterol levels, elevated low density lipoprotein, and reduced high density lipoprotein. This suggests that coronary artery disease will worsen in diabetic women who take the pill, although this is more of a problem in adults. Recent studies also implicate the progestin component in some of the lipogenic effects, especially norgestrel and its active form levonorgestrel. Some of the changes may be reversed by exercise such as consistent running.[56] In addition, there are disturbing studies by Steel and Duncan noting that even young adult diabetic women who take the pill develop increased vascular complications such as cerebrovascular accidents and increased progressive nephropathy and retinopathy.[57,58] These reports note that even those who have good metabolic control are at increased risk.

Alternative contraceptive methods, therefore, usually are offered to diabetic teenagers, especially if hyperlipidemia is present. The minipill, medroxyprogesterone acetate, and barrier methods should be considered. The intrauterine device is not recommended because of the increased risk of pelvic infections and higher failure rate as a result of interaction with the diabetic endometrium.

Epilepsy

Seizure disorders are a relative contraindication to pill use.[2] Although epileptic youths may need higher doses of anticonvulsants, this alone is not enough to withhold oral contraceptives. Those with poor epileptic control, however, are not candidates for oral contraceptives. A more serious problem is drug interactions that result in interference with oral contraceptives (Table 18-11).[21,50-52] This may be due to an anticonvulsant drug–induced increase in liver microsomal enzymes, which results in increased pill metabolism. Although the actual risk is unknown, the increase is such that alternative contraceptive methods should be considered, especially in view of the possible teratogenic effects of antiseizure medications. Therefore, care must be taken when considering a youth who uses other drugs for oral contraceptives. In addition, the pill may potentiate the effect of drugs such as reserpine, corticosteroids, and chlordiazepoxide. Contraceptive drug interactions decrease the effect of certain drugs such as tricyclic antidepressants, insulin, methyldopa, guanethidine, and anticoagulants.

In addition, many neurologic disorders have developed or worsened with the use of oral contraceptives.[2] These anecdotal reports include systemic lupus erythematosus, Raynaud's disease, pseudotumor cerebri, chorea, and dizziness. Beaumont postulated that oral contraceptives induce antibodies (Beaumont protein-GAP) in a subgroup of pill users.[59] This may imply an increased risk for collagen vascular diseases in women taking oral contraceptives. However, other investiga-

tors have not confirmed the presence of GAP.[59] Also, there is conflict over the pill's effect on arthritis. Some reports have found a worsening of rheumatoid symptomatology, whereas more recent studies note the pill's protective effect on the development of rheumatoid arthritis.[60] Multiple sclerosis and neurofibromatosis also have worsened in women on the pill.

Migraine Headaches

It is well known that the pill can cause and/or worsen migraine headaches.[17] There also are a few anecdotal reports of migrainoid women who developed cerebrovascular accidents while on oral contraceptives. In 1969, Ask-Upmark et al reported on a 17-year-old girl with migraine headaches who developed a cerebrovascular accident after being on a high-estrogen pill for 1.5 years; she developed hemiplegia and died.[61] Hence, clinicians often have listed migraine headaches as a contraindication to the pill.

Should a clinician prescribe the pill for a migrainoid youth? "Mild" migraines need not be an absolute contraindication because the headaches do not inevitably get worse. A history of severe migraines, however, should preclude the use of the pill. If the teenager's migraine or the aura associated with it worsens, the pill should be stopped immediately. Teenagers with a history of prolonged auras (hemiplegic or ophthalmoplegic types) should not use the pill. Careful monitoring clearly is essential. There is, however, no association between oral contraception and simple tension headaches.

Liver Disorders

The pill is absolutely contraindicated in the teenager with active liver disease.[62,63] A history of hepatitis is not a deterrent in itself if liver function has returned to normal. A liver screening profile usually is not necessary for teenagers who want the pill unless the history indicates possible liver dysfunction. The literature of the 1970s established a small but significant association of oral contraceptives with the development of benign hepatic adenomas.[62] Focal nodular hyperplasia or hepatic cell adenoma can develop, especially with mestranol-type pills, and resolve after the pill is discontinued. Occasional areas of nodular hyperplasia can rupture in the liver or peritoneum, inducing a syndrome of variable abdominal pain, right upper quadrant mass, right shoulder pain, and even shock. Menstruation can encourage tumor bleeding, and chronic pill use may induce tumor development. Hepatic cell adenomas are the only type of pill-induced tumors that have been identified since the pill was marketed and have an estimated annual incidence of 3.4 per 100,000 pill users.[62]

Cancer

Despite extensive research over the past 20 years, there is only limited evidence that oral contraceptives cause cancer.[64–68] The only neoplasm associated with the pill is benign hepatic adenoma.[62,63] Thus, teenagers can be assured that they are not at known risk for developing any type of carcinoma because of the pill. There is no clear evidence linking the pill with pituitary adenomas,[45,46] endometrial cancer,[69,70] ovarian cancer,[71] or breast cancer.[72,73] In fact, the pill seems to have a protective effect against cancers of the ovaries, endometrium, and breasts.[60,71] The sequential pills, however, were removed from the market in the 1970s because of a possible link to endometrial carcinoma.[21] In addition, a recent small study from Los Angeles suggests a possible increased risk of breast cancer in young adults who are on progestin-predominant oral contraception for several years before first becoming pregnant.[74] However, a recently published study does not agree.[75] Further studies certainly are needed to clarify these preliminary data.

Moreover, there is no proven link between oral contraceptives and cervical cancer. Cancer of the cervix seems seems to have multiple causes, including early sexarche, frequent sex partners, and genital herpes.[76] Abnormal cervical cytology occasionally is noted in sexually active teenagers. Therefore, periodic screening of all sexually active youths is recommended. A recent study from Oxford suggests a possible link between cervical cancer and oral contraception.[77] It is based on a 10-year follow-up study of 6838 women who used the pill and 3154 who had IUDs. Although further

research is necessary, the study underscored the need for periodic Papanicolaou screening. Finally, there is some evidence that the pill can worsen malignant melanomas, a rarity in teenagers.[78]

Miscellaneous Effects of Oral Contraceptives

Gynecologic Effects

Teenagers on the pill may develop increased benign cervical polyposis and cervical erosion, so a yearly Pap test is recommended. They also have more frequent *Candida albicans* vaginitis as a result of a pill-induced increase in the glycogen content of vaginal epithelium, which enhances yeast growth.[79] Standard antifungal therapy usually is effective, and rarely does the pill need to be stopped because of resistant monilial infections (Table 18-7). Benign galactorrhea occasionally develops in teenagers on the pill.[17] As previously noted, there is no evidence that the pill induces prolactin-secreting pituitary adenomas.[45,46] However, some authorities do recommend discontinuation of the pill for galactorrhea. Also, lactation remains a relative contraindication to pill use. There is a reduction in the amount of breast milk as well as less protein and lipids.[67,80] The hormonal contents can appear in the milk, resulting in rare reports of infant gynecomastia and vaginal cornification. Although infrequent in teenagers, leiomyomata tend to worsen under the hormonal influences of the pill.[17] Finally, the beneficial gynecologic effects of oral contraceptives should be noted, which include considerably less benign breast disease, ovarian cysts, and pelvic inflammatory disease (Table 18-10).[60,81,82]

Genitourinary Effects

Women on the pill have an increase in bacteriuria and urinary tract infections.[17,67,83] This may be the result of pill-induced bladder trabeculations and/or increased coital activity. The pill is not indicated in teenagers with renal disease because of its potential hypertensive effects.[9,17,38] Other contraceptive methods such as the minipill or barrier methods should be used.

Endocrine Effects

There is no evidence that the pill oversuppresses the hypothalamic-pituitary-gonadal axis in teenagers and causes limited growth or postpill amenorrhea.[25] Thyroid functioning is normal, but there is an increase of total serum thyroxine because of increased binding protein.[84] If there is a serious question about thyroid functioning, it is best to stop the pill and check the appropriate laboratory tests in 2 or 3 months. Likewise, adrenal function remains normal, but there is an increase in cortisol-binding globulin, with a resultant rise in plasma cortisol level.[85] There also may be a reduced ACTH and pituitary reserve. Thus, oral contraceptives should not be given to teenagers with ACTH deficiency or hypopituitarism.[66]

Gastrointestinal Effects[2]

Pill-induced hepatic adenoma and focal nodular hyperplasia have been discussed. Teenagers who take the pill have a small but significantly increased risk of gallstones.[19,49] Occasionally, oral contraceptive use may lead to pancreatitis, especially if the patient has hyperlipidemia. Therefore, the pill is clearly contraindicated in youths with elevated triglycerides, especially those who are diabetic. There are anecdotal reports of adults on the pill who subsequently develop mesenteric vascular disease, hepatic vein obstruction (Budd-Chiari syndrome), and even ulcerative colitis. This points to examination prior to starting the pill for women who have abdominal pain. If pain should develop while a woman is using an oral contraceptive, she should be monitored diligently.

Dermatologic Effects[9,17,67,83-85]

Melasma (chloasma) can occur in 3–8% of pill users, occuring most often in women with dark complexions. If this happens, the pill should be stopped immediately. Melasma may fade slowly or be permanent. Acne vulgaris may worsen with 30- to 50-μg estrogen pills but usually improves with standard acne therapy (Table 18-7). Oral contraceptives with 80–100 μg estrogen may improve acne but usually are not recommended for teenagers

because the risk of thromboembolic phenomena may be too great. Porphyria also is a contraindication because it can develop or worsen under the pill's influence. Other dermatologic conditions that can be induced or made worse by the pill include acanthosis nigricans, alopecia, spider nevi, erythema nodosum, telangiectasia, and angioneurotic edema.

Hematologic Effects

Menorrhagic-induced anemia often is improved in pill users because they have a more regular menstrual flow with less blood loss.[60,86] However, folic acid and vitamin B_{12} deficiences (Table 18-5) as well as unusual cases of megaloblastic anemia have been reported in pill users. In view of an increased risk of sickling, oral contraceptives should be avoided in teenagers who have sickle cell anemia and sickle cell C disease.[87,88] The intrauterine device may not be suitable for sicklers either because of its increased infection risk.

Other Effects[2,13,17,21,23,35,49,54,66]

Oral contraceptives are contraindicated for teenagers who have retinal or optic nerve disorders. There have been various reports of retinal vessel spasm and/or occlusion, optic neuritis, corneal and retinal edema, retrobulbar neuritis, and worsening myopia.[84] Increased fluid retention may make it difficult for some teenagers on the pill to wear contact lenses.[14] Attention to the ophthalmologic system is recommended for any teenager on the pill.Eustachian tube dysfunction and worsening of otosclerosis also have been reported, as has an increased incidence of gingivitis.

There is general agreement that a small number of women on the pill become clinically depressed.[2,89] However, not everyone believes it is a result of the pill.[14,21,83] A deficiency in pyridoxine with resultant tryptophan metabolism dysfunction is often suggested but has not been proven as the cause.[89] Some recommend the addition of vitamin B_6 supplements as a precautionary measure. If severe depression develops, the pill should be stopped pending a full evaluation.

Teenagers who get pregnant while using the pill have an increased risk of having infants with congenital anomalies. Cardiac, limb reduction, vertebral, and anal defects have been reported.[90] There was a disturbing report by Carr noting a doubled rate of chromosomal abnormality in the spontaneous miscarriages of postpill users compared with those of nonpill users.[91] Although the pill is considered a mild teratogen, girls who become pregnant while taking it are not necessarily advised to have an abortion[67] because many believe it is not a proven cause of teratogenesis in humans.[92] Lactating teenagers who take oral contraceptives are not subjecting their infants to an increased risk of growth delay. Nor do teenagers who use oral contraceptives adversely affect later pregnancies, although there has been an increased incidence of twins reported in postpill users.[2]

Low-Estrogen Oral Contraceptives

An important trend during the past decade is the development of low-estrogen pills and, more recently, low-progestin contraceptives.[93,94] The current recommendation is that girls not be given pills with an estrogen content of more than 50 μg. The "low-dose pill" (35–50 μg of estrogen) or "micropill" (20–35 μg of estrogen) reduces metabolic effects. There is a tendency for increased breakthrough bleeding, especially with the 20-μg estrogen pill.[95] There also may be an increased pregnancy risk with the 20-μg estrogen pill, so this type is not recommended for teenagers. Table 18-12 lists the low-dose pills available in the United States. It also should be noted that the low-estrogen pills are not as effective in girls who are poorly nourished because the body is unable to absorb an adequate amount of hormone. The usual recommendation for the teenagers is a pill with 30–35 μg (up to 50 μg) of ethinyl estradiol and 0.15–1.5 μg progestin.[25,95] The progestin with the greatest worldwide acceptance is norgestrel, and the most popular brands often combine low-dose ethinyl estradiol with low-dose norgestrel.[12,94] Pills with norethindrone also are popular. Many clinicians outside the United States prefer the active norgestrel derivative levonorgestrel (d-

Table 18-12. Low-Estrogen Birth Control Pills.

Type	Name	Estrogen (mg)	Progestagen (mg)
Combination pills with greater than 50 μg estrogen	Enovid-E[a]	Mestranol, 0.1	Norethynodrel, 2.5
	Ovulen[a]	Mestranol, 0.1	Ethynodiol diacetate, 1
Minipill	Micronor	—	Norethindrone, 0.35
	Nor-Q.D.	—	Norethindrone, 0.35
	Ovrette	—	Norgestrel, 0.075
Combination pills with 50 or less μg of estrogen	Ovral[b]	Ethinyl estradiol, 0.05	Norgestrel, 0.5
	Demulen	Ethinyl estradiol, 0.05	Ethynodiol diacetate, 1
	Norinyl 1 + 50	Mestranol, 0.05	Norethindrone, 1.0
	Norlestrin 1/50	Ethinyl estradiol, 0.05	Norethindrone acetate, 1.0
	Norlestrin 2.5/50	Ethinyl estradiol, 0.05	Norethindrone acetate, 2.5
	Brevicon (Modicon)	Ethinyl estradiol, 0.035	Norethindrone, 0.5
	Loestrin 1/20[b]	Ethinyl estradiol, 0.02	Norethindrone acetate, 1.0
	Loestrin 1.5/30[b]	Ethinyl estradiol, 0.03	Norethindrone acetate, 1.5
	Lo/Ovral[b,c]	Ethinyl estradiol, 0.03	Norgestrel, 0.3
	Ortho-Novum 1/35	Ethinyl estradiol, 0.035	Norethindrone, 1.0
	Ortho-Novum 1/50	Mestranol, 0.050	Norethindrone, 1.0
	Ovcon-35	Ethinyl estradiol, 0.035	Norethindrone, 0.4
	Ovcon-50	Ethinyl estradiol, 0.050	Norethindrone, 1.0
	Nordette[b,c]	Ethinyl estradiol, 0.030	Levonorgestrel, 0.15

[a]Estrogen dominant.
[b]Progestin dominant.
[c]Norgestrel is a mixture of levo norgestrel and dextronorgestrel.[94] Only the levomolecule is active. Since 0.30 mg of norgestrel is equal in potency to 0.15 mg levonorgestrel, Lo-/Ovral and Nordette should be equivalent.

norgestrel). Current research is attempting to lower norgestrel and norethindrone dosage to the lowest point where efficacy is combined with minimal side effects. A proposed combination that is gaining worldwide acceptance in the 1980s is 30 μg of ethinyl estradiol with 150 μg levenorgestrel or 0.3 mg norgestrel, such as the combinations found in Nordette or Lo-Ovral. (Table 18-13).[96]

Bi(Tri)phasic Oral Contraceptives

In an attempt to reduce the hormonal content of oral contraceptives, both a biphasic and a triphasic pill have been developed.[97-100] The biphasic pill consists of a two-fixed-ratio combination of an estrogen and progestin, which are taken sequentially. Ortho-Novum 10/11 are white tablets that are taken for 10 days and then followed by peach tablets taken for days 11 through 21.[19] The white tablets are equivalent to Brevicon or Modicon (0.5 mg norethindrone and 35 μg ethinyl estradiol). The peach tablets are equivalent to Ortho-Novum 1/35 (35 μg ethinyl estradiol plus 1 mg norethindrone). This is an attempt to prevent ovulation while at the same time more closely resembling the normal menstrual cycle, during which a higher dose of progesterone appears in the second half of the cycle. Whether it has any real advantage over more traditional low-estrogen and low-progestin pills remain to be seen. This new pill also may have more breakthrough bleeding.[10]

In Europe, and now available in the United States, a triphasic pill has been developed that

Table 18-13. Contraindications to IUD Placement.

1. Pelvic infection (acute cervicitis or pelvic inflammatory disease)
2. High risk for sexually transmitted diseases
3. Cervical or uterine hypoplasia
4. Uterine malignancy
5. Severe menorrhagia/anemia
6. Severe dysmenorrhea
7. High risk for bacterial endocarditis
8. Recent postpartum endometritis
9. Recent septic abortion
10. History of ectopic pregnancy
11. Bleeding disorders

alters the amount of ethinyl estradiol and levonorgestrel.[97,98] For the first 6 days the pill contains 30 μg ethinyl estradiol and 50 μg progestin; there is 40 μg estrogen and 75 μg progestin for days 7 through 11, and 30 μg estrogen with 125 μg progestin for days 12 to 21. This is an attempt to simulate the menstrual period while inhibiting ovulation. It is an effective contraceptive and also may cause less irregular menstrual bleeding than found with the traditional low-estrogen pills. However, although some girls may see a decrease in acne secondary to the pill, this pill may increase dysmenorrhea, breast tenderness, and serum triglycerides.[99]

The MiniPill

Minipills contain only a progestin and do not reliably inhibit ovulation.[40,101] Contraception is caused by various "secondary" mechanisms such as a thickening of the cervical mucus that makes it more difficult for sperm to penetrate, an alteration of corpus luteum function, an altered endometrium that inhibits blastocyst implantation, and an increased transport of the ovum through the oviduct. Table 18-12 lists the three brands sold in the United States. Studies have noted a reduced risk of thromboembolic phenomena, metabolic alterations, and hypertension.[2] There is no interference with lactation, and some studies report improvements in dysmenorrhea and premenstrual tension syndrome. Therefore, the minipill may prove a valuable alternative for sexually active teenagers who have a contraindication for the estrogen component of the combined pill, but nevertheless want an oral contraceptive.

Some clinicians do not recommend the minipill for teenagers because of an increased pregnancy rate (one to three pregnancies per 100 woman-years of use) and frequent breakthrough bleeding and amenorrhea.[21] There also have been reports of increased incidences of ectopic pregnancy and some minor weight gain (3 to 6 lb).[26]

Intrauterine Device (IUDs)

The use of a metallic or plastic device within the uterus to prevent pregnancy has been controversial since its introduction by Richter and Graefenberg.[102] Although not as effective as oral contraceptives in large series, the IUD's rate of one-half to five pregnancies per 100 woman-years of use makes it an acceptable method for some teenagers.[103,104] The IUD works by inhibiting blastocyst implantation. Thus, some are ethically opposed to its primary abortive mechanism. There also is spermicidal activity when copper is added.

The various IUDs can be classified as hormonal (Copper 7, Copper T, or Progestasert) and nonhormonal (Lippes Loop, Saf-T-Coil, Dalkon Shield). In general, the larger devices that have increased surface areas have lower pregnancy rates but tend to cause more pain and bleeding. The normal menstrual flow of 35 ml per period can be increased to 50 or 60 ml with the Copper 7 and 80 ml or more with the Lippes Loop. Usually, the copper devices are preferred for nulliparous teenagers because they are small, easy to insert (usually early in the menstrual flow), are less likely to be expelled, and have acceptable efficacy. Various types of devices that contain more copper are being studied and include T Cu 200, T Cu 300, and T Cu 380 A. The copper types usually stay in place after birth or abortion better than the others. The Progestasert IUD is associated with blood loss less than the preinsertion menstrual loss but is more expensive than the Copper 7 and must be replaced every 1 to 2 years.

The numerous contraindications to IUD use are listed in Table 18-13,[102] while Table 18-14 lists complications.[102,105] Pain during insertion can be reduced by using local anesthesia such as a paracervical block. Expulsion rates after 1 year are five to 15 per 100 woman-years, and

Table 18-14. Complications of IUD Use.

1. Pain during insertion
2. Increased menorrhagia with anemia
3. Increased dysmenorrhea
4. IUD expulsion
5. Inability to find the IUD string
6. Perforation of the uterus with peritonitis
7. Bowel perforation
8. Pregnancy (increased maternal and fetal morbidity)
9. Ectopic pregnancy
10. Spontaneous abortion
11. Pelvic infections
12. IUD embedment with resultant endometrial necrosis
13. Bacterial endocarditis

forced removal secondary to bleeding and/or pain also is five to 15 per 100 woman-years of use.[2] Removal for other medical reasons is three to nine per 100 woman-years of use, while removal for other reasons is one to six. A lost IUD is less of a problem with polyethylene IUDs than with copper types, which can incite serious inflammation. There is more midcycle bleeding or spotting and increased ectopic pregnancy rates noted with the progestin-releasing IUD (Progestasert). A copper type is recommended for teenagers because of its lower complication rates.

The IUD is a major precipitant for pelvic inflammatory disease, whether initiated by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.[105–109] Multiple studies have noted that IUD users have a three- to ninefold increase in pelvic infections, especially pelvic inflammatory disease. Teenagers at major risk are those who have multiple partners or promiscuous partner(s). Unfortunately, many teenagers are at high risk of developing pelvic inflammatory disease and its many complications, which include sterility, ectopic pregnancy, and chronic pelvic pain.[18,19] Other pelvic infections associated with the IUD include pelvic actinomycosis and ovarian abscesses. Pelvic inflammatory disease rates are much higher with the Dalkon Shield* than with the copper types.[107] Thus, the IUD probably should not be recommended for the majority of teenagers. However, a girl who is at minimal risk for pelvic infections and wants an IUD should be given one. In general, the younger teenager who often changes partners is not a good candidate, whereas the older teenager with one stable partner might be considered.

Barrier Methods

Diaphragm

The classic barrier method consists of a rubber cap that has a metal spring in its rim.[110–119] When inserted correctly into the vagina it is held in place by the muscles, the rim spring tension, and the pubic bone. The nulliparous youth with good vaginal tone retains the diaphragm well if correctly fitted. Contraception is the result of the device blocking sperm from entering the cervix and from the spermicidal action of contraceptive cream or jelly that is put on the diaphragm.[114] The diaphragm usually is inserted an hour or so prior to coitus and left in place for 6–8 hours after intercourse.[19] More vaginal contraceptive must be added for subsequent intercourse or if the diaphragm has been in place more than 2 hours prior to coitus. The failure rates with this method vary anywhere from an acceptable 2.4 pregnancies per 100 woman-years of use to an unacceptable 30 per 100 woman-years. Motivated teenagers who use the diaphragm correctly every time have good rates.[111,113,116] This is an especially good method for the motivated girl who has infrequent sexual encounters.

Most teenagers, however, do not use this method because of the requirements necessary for its success; persons using the diaphragm must be knowledgeable and comfortable with their bodies, must recognize their interest in sex, and must acquire the motivation and skill necessary to use it correctly.[117] Unfortunately, many girls feel strange touching themselves intimately, an ability necessary to use a diaphragm. Moreover, many youths feel that the use of a diaphragm is an admission of an interest in sex greater than their partner's. Barrier methods such as the diaphragm should be encouraged, however,[115,118] because they can provide effective contraception with minimal side effects. Side effects include infrequent burning of vaginal walls or penis, rare allergy to rubber or vaginal contraceptives, dyspareunia if a diaphragm is too large, and foreign body vaginitis if the diaphragm is left in more than 1 or 2 days. If discomfort occurs with one brand of vaginal spermicide, another brand usually can be tolerated. Sometimes a diaphragm is a good interim method such as when an IUD is removed and a girl is awaiting the correct time in her cycle to begin the pill. A few studies of adults have suggested that the diaphragm may offer some protection from cervical carcinoma.[2]

An important aspect of prescribing a diaphragm is fitting the teenager with the correct size.[112,119] Four types of diaphragms are available (Table 18-15).[116] Most teenagers do well with the coil-spring or flat-spring type.

*The Dalkon Shield has recently been removed from the market.

Table 18-15. Types of Diaphragms.

Coil-spring diaphragm A round, spiral-coiled metal wire is placed in the rim. It folds in one place and is acceptable for most youth.
Flat-spring diaphragm (Mensinga) Similar to coil-spring diaphragm but firmer. It is helpful in women who have a pointed cervix and/or anteverted uterus.
Arching-spring diaphragm (Findley) This has a double metal spring in the rim which creates an arch when the rim is compressed. It is suggested for those with poor muscle tone and when the cervix is posteriorly directed.
Matrisalus diaphragm (Bowbent) This has a strong, flat steel band that is curved and inserted in the rim. It is suggested for individuals with a cystocele or vaginal wall relaxation.

Contraindications to diaphragm use are listed in Table 18-16.[114] However, the main problem usually is lack of motivation or refusal to use it. The fitting process can be difficult for girls who normally are embarrassed and uncomfortable with their bodies. Thus, the clinician should do the briefest examination possible, checking for the largest size that will correctly fit in the vagina and extend from the posterior fornix to below the pubic bone.

The diaphragm's dome is placed convex to the vaginal aperture while the cervix is covered.[116] The girl should not feel it, but occasionally her partner will notice it. The largest size comfortably accepted is important because the vagina's size increases during coitus. Moreover, vigorous coitus with the female on top may cause it to become dislodged. The clinician also must realize that vaginal muscles can be tense during the first fitting; so the youth should return with the prescribed diaphragm, enabling the clinician to recheck the size and affirm that she knows how to properly use it. Sizes vary from 55 to 105 mm in diameter, but most use a 60- to 85-mm diaphragm. Although the diaphragm can last up to 2 years, the size should be rechecked if there is a 10- to 15-lb weight change, if she has vaginismus, if the girl was a virgin at the first fitting, if she has a midtrimester abortion, or if there are other reasons to consider the need for a different size.[110,114,117]

A variation of the diaphragm is the cervical cap.[116,119,120] This is a small caplike device that fits only over the cervix. It is an unusual youth who will use this contraceptive. Currently, the caps on the market are not recommended because they dislodge easily and tend to cause a strong vaginal odor. In addition, studies have found unacceptably high pregnancy rates.[121–124] However, current research using newly designed cervical caps may make the device an acceptable method in the near future.[123] The new cap is made of a plastic mold that is fitted for each patient and held in place by surface tension instead of the elastic or suction pressure of current caps. Spermicidal agents are not used with this new cap because it is made of a thermoplastic material that causes sperm immobilization. The cap can be worn most times except during menstruation.[124] Whether the cap or diaphragm tends to cause more toxic shock syndrome remains to be seen.[110]

Table 18-16. Contraindications to Use of the Diaphragm.

1. Limited motivation
2. Perineal tears
3. Allergy to rubber or spermicides
4. Short anterior vaginal wall
5. Complete uterine prolapse
6. Severe anteversion
7. Severe retroversion

Condoms

There are many types of quality condoms that allow the male to contribute to contraceptive

Table 18-17. Reasons for Limited Condom Acceptance.

1. Male refusal to accept contraceptive responsibility
2. Need for appropriate technique with each coitus
3. Cost
4. Reduced penile sensation during intercourse
5. Disruption of foreplay required to place the condom
6. Religious beliefs
7. Stigma of condom in association with loose morals and sexually transmitted diseases
8. Limited acceptance in recommendation by the health care profession
9. Limited acceptance by pharmacists to overtly display the condom

Table 18-18. Advantages of the Condom.

1. Effective contraceptive potential
2. Does not require a prescription
3. Some protection from sexually transmitted diseases
4. Very few side effects
5. Allows the male to contribute to contraceptive responsibility
6. Many types of high quality are now available
7. Can aid in improvement of dyspareunia (lubricated)
8. Aids with premature ejaculation
9. Possible protective effect for cervical cancer[117,125]

Table 18-19. Advantages of Vaginal Contraceptives.

1. When combined with the diaphragm or condom, can give effective contraception
2. When combined with the condom, allows the couple to share in contraceptive responsibility
3. No prescription required
4. Limited cost
5. Side effects are few
6. Suggested for those with limited coital encounters
7. Aids in dyspareunia
8. Offers *some* protection from various sexually transmitted microorganisms (*N. gonorrhoeae, C. trachomatis, T. pallidum, C. albicans, T. vaginalis*, herpes simplex).

responsibility.[125] The efficacy of condoms varies from 3 to 30 pregnancies per 100 woman-years of use. Although often ignored by teenagers, the condom is one of the more popular contraceptive methods in the world.[110] Table 18-17 outlines reasons for its avoidance and Table 18-18 lists the advantages of this technique.[117] The prophylactic can be an excellent method and should not be ignored.[110,125–128] Sometimes its partial protection against sexually transmitted diseases is a convincing argument for its use.

Vaginal Contraceptives

Vaginal contraceptives include creams, jellies, powders, pastes, foaming tablets, suppositories, contraceptive film, and sponges.[129–131] Contraceptive efficacy ranges from 1.3 to 38 pregnancies per 100 woman-years of use. Contraception is based upon surface active chemicals (octoxynol or nonoxynol-9) that reduce the surface tension of the sperm, thereby breaking down the cell wall.[119] Bactericidal agents (ricinoleic acids or phenylmercuric acetate) also can be present.[117] The vaginal contraceptive is best if used in combination with a diaphragm or condom.[110]

Table 18-19 outlines some of the advantages of vaginal contraceptives. In unusual cases, allergic reaction to a specific agent is possible, but this is usually rectified by changing brands (Table 18-20). Cystitis occurred in one case when a suppository was placed into the urethra.[2] A recent study has suggested that vaginal contraceptives may lead to an increase in congenital anomalies, presumably by damaging instead of killing sperm.[132] This, however, has not been accepted or confirmed by other investigators.[133] Moreover, variable protection from numerous sexually transmitted diseases has been observed in several studies (Table 18-19).[108,110,114,119] In general, foam seems to be the best of this group because of its better coverage. Cream is the next best. Proper technique is necessary for maximizing contraceptive efficacy. The vaginal contraceptive should be inserted high into the vagina as much as 1 hour before anticipated intercourse. Generally, 15 to 30 minutes should be allowed for these agents to melt. Suppositories should be placed near the external cervical os. Additional agent must be added for more coitus. Douching or bathing should be delayed at least 6 hours after intercourse. The contraceptive film is a water-soluble plastic film inserted into the vagina prior to coitus. Unfortunately, many teenagers reject vaginal contraceptives for the same reasons they do not accept the diaphragm.

Collagen Sponge

This is a disposable polyurethane sponge (Today-VLI Corp.) that comes in one size and does not require a prescription.[110,119,134,135] It recently was introduced as a concave-shaped sponge that fits over the cervix. It blocks sperm from reaching the external os, absorbs seminal fluid, and kills sperm because the hydrophilic foam contains 1 g of nonoxynol-9. Moistened with 2 tbsp. of water and inserted up to 2 days before coitus, the sponge must be left in at least 6 to 8 hours after intercourse. Pregnancy rates vary but generally are not as good as those found with the diaphragm when properly used.[135] The sponge can cause vulvar

Table 18-20. Various Brands of Vaginal Contraceptives.

Name	Active Ingredient	How Supplied
Encare Oval Vaginal Suppositories	Nonoxynol-9	Box of 12 inserts
Because Birth Control Foam	8.9% nonylphenoxyl-polyoxyethylene ethanol + 0.2% benzethonium chloride	10 g with applicator
OrthoCreme Contraceptive Cream	Nonoxynol-9	2.46-oz, tube with applicator
OrthoGynol Contraceptive Jelly	p-Diisobutylphenoxy-polyethoxyethanol	2.85-oz tube with applicator
Ramses 10-hour Vaginal Jelly	Dodecaethyleneglycol-monolaurate	3 oz. with applicator
Loromex Contraceptive Foam	Nonoxynol-9	22-g can with applicator
Loromex[II] Contraceptive Cream	Octoxynol	2.65 oz. with applicator
Loromex[II] Contraceptive Jelly	Octoxynol	2.85 oz. with applicator
Semicid Vaginal Contraceptive Suppositories	Nonoxynol-9	Packages of 3, 10, and 20
Delfen Cream	Nonoxynol-9	2.46-oz. tube with applicator
Delfen Foam	Nonoxynol-9	0.70-oz. vial can with applicator
Emko Foam	8.0 Nonylphenyoxy-polyoxyethylene ethanol + 0.2% benzethonium chloride	45-g aerosol with applicator
Others		

rash, genital pruritus, and odor if left in too long. It has not been proven whether the incidence of toxic shock syndrome is increased.[136] Because polyurethane can be changed in vitro to a known carcinogen (2,4-toluenediamine), there is some question as to whether there might be a carcinogenic effect associated with the sponge.[135] However, this is only a theory. Thus, the collagen sponge seems to be a new, acceptable barrier contraceptive that may be suitable for some teenagers. Its actual advantage(s) over other barrier techniques remains to be shown.[137] The fact that it can be left in place longer and inserted earlier than the diaphragm makes it an attractive alternative for some teenagers.[119]

Injectable Contraceptives

The only contraceptive method that when surveyed in large studies has the same effectiveness as the combined birth control pill is depomedroxyprogesterone acetate (Depo-Provera).[138–141] Both these methods have pregnancy rates under one per 100 woman-years of use. There are other long-lasting injectable contraceptives, including norethindrone enanthate (Noristerat) and Lynestrenol, which are used in other parts of the world.[141] Depo-Provera is given intramuscularly at a dose of 150 mg every 3 months. It prevents ovulation by stopping the midcycle LH rise, thins the endometrium so that blastocyst implantation is inhibited, and increases cervical mucus viscosity, which reduces sperm penetration.[138] This is an excellent contraceptive method used by many throughout the world.[49,139] Often recommended when the estrogen in oral contraceptives is contraindicated, Depo-Provera has a minimal effect on blood pressure and lactation.

A major side effect is irregular menstrual bleeding and eventual amenorrhea, which occurs in up to 23% after 1 month and in 69% 2 years after its initiation.[9] Approximately 15% have an abnormal glucose tolerance curve, and 5% develop miscellaneous features such as nausea, emesis, nervousness, weight gain, and headache. Although considered safe and effective by health care professionals throughout the world, the Federal Drug Administration (FDA) has not approved its general use because of unproven concerns about the

possible risk of congenital anomalies, a possible increased risk of breast nodules and carcinoma, and the known high incidence of menstrual irregularity.[138] However, it remains a contraceptive method worthy of consideration. Mentally ill or mentally retarded teenagers at high risk of pregnancy could be given Depo-Provera.[140] The absence of menses in some teenagers may be a benefit. Those with cyanotic heart disease, history of thromboembolic phenomena, sickle cell anemia, and other chronic illness also would be candidates for this contraceptive method.[2] However, the need for repeated injections and the resultant menstrual irregularity limit the number of teens for whom this is an acceptable method.[140] In the future, progestins in other forms such as a levonorgestrel IUD, skin implants, vaginal rings, and even a once-a-month oral progestin pill will be marketed.[101,141]

Postcoital Contraceptives

Estrogens or other contraceptive agents taken after coitus normally are used only in emergencies such as the case of sexual assault.[142] This method prevents blastocyst implantation. Diethylstilbestrol (DES) is FDA-approved and given at a dose of 25 mg by mouth twice daily for 5 days; it should be started within 72 hours of coitus.[35] Pregnancy rates are very low with this method (0.3 to 0.03%).[9] Pregnancy should be ruled out prior to prescribing DES because of its well-known effects on offspring. Some health care professionals recommend signed consent prior to its prescription, and abortion may be recommended if pregnancy already has occurred when DES is taken.[18] The actual risks to the fetus, however, are not known. In addition, nausea and emesis occur in 50% of patients, the result of the recommended dose's estrogen content. This may be partially relieved by taking the drug during meals and/or giving an antiemetic. Other side effects include a probable increase in ectopic pregnancy and/or menorrhagia with the menstrual period following the episode. One case of pulmonary edema also has been reported.[2]

Table 18-21 outlines various postcoital contraceptives.[9] Postcoital insertion of a copper-type IUD is an effective method that avoids estrogen side effects.[102,143] New methods under study include dl-norgestrel (l mg) with ethinyl estradiol (100 mg) given 12 hours apart, a progesterone receptor antagonist that causes an interruption in blastocyst implantation, and synthetic agonistic peptide analogs of gonadotropin-releasing hormone that cause luteolytic interception.[144] While these other methods are generating more interest, DES and copper IUDs are the primary current postcoital contraceptives used for teenagers.

Table 18-21. Postcoital Contraceptives.

1. DES, 25 mg by mouth twice daily for 5 days.
2. Ethinyl estradiol, 5 mg by mouth for 5 days.
3. Conjugated estrogens, 30 or 50 mg by mouth for 5 days.
4. Conjugated estrone sulfate, 100 mg by mouth for 5 days.
5. Ethinyl estradiol (50–100 mg) with 0.5–1.0 mg norgestrel. These are given together on two occasions, 12 hours apart.
6. Postcoital IUD insertion (copper device).
7. Progesterone receptor antagonists (under research).
8. Synthetic agonistic peptide analogs of gonadotropin-releasing hormone (under research).

Miscellaneous Contraceptive Methods

Abstinence

Any discussion of contraception for teenagers should include abstinence as an option.[18,19,35,117] The pregnancy risk from a single coital episode is 2–4%; obviously the risk from abstinence is 0%. Confidential counseling by the health care professional can reassure the youth that she doesn't have to have sex and that abstinence can be a healthy physiologic and psychologic alternative.

Periodic Abstinence (Rhythm Method)

Various methods have been used that attempt to prevent pregnancy by abstaining from coitus in the periovulatory period.[145–147] The Ogino-Knaus method (calendar method) is based on three important concepts: ovulation occurs 14 days before the next menstruation, the viability of the oocyte is about 24 hours following ovulation, and the fertile life span of

Table 18-22. Five Phases of Cervical Mucus Changes.

1. Phase 1: dry (no mucus)—early postmenstrual days
2. Phase 2: increasing amount of sticky mucus
3. Phase 3: copious amount of clear, slippery mucus (periovulatory stage)
4. Phase 4: reduced amount of sticky mucus
5. Phase 5: clear, watery mucus (premenstrual time)

sperm in the female genital tract is 3 to 4 days.[147] Thus, the unsafe days are anywhere from menstrual day 9 through 18. Unfortunately, the latter two concepts remain unproven. Contraceptive methods based on these principles do not prevent pregnancy for most teenagers. Teens often have limited knowledge of their own physiology and are poorly motivated to use these methods every time they have sex. The temperature method—based on a temperature increase of 0.3–0.5 degrees Centigrade (0.5–1.0 degrees Fahrenheit) at ovulation—doesn't work for most teenagers.

Recently, there is increased interest in the Billings or ovulation method which is based on menstrual cycle alterations in the cervical mucus. Five phases occur (Table 18-22) during which there is a gradual increase in cervical mucus until at the periovulatory period it looks like raw egg whites (spinnbarkeit).[147,148] Coitus is avoided at this time and/or for a number of days before and after.

Studies have shown that this is a reliable method for some highly motivated women.[147,148] However, it does have a variable contraceptive efficacy record that ranges from five to 40 pregnancies per 100 woman-years of use.[2] Many teenagers have irregular menses, limited motivation, and inadequate knowledge of their bodies to be able to use this contraceptive method. Thus, periodic abstinence generally is not recommended for adolescents.[2,18,35] However, some older teenagers who are motivated can use this method properly.

Lactation

Breast-feeding can prolong postpartum amenorrhea but should not be relied upon for effective contraception.[149,150] Many females ovulate before menstruation returns and 3–10% of lactating adult women who do not use contraception become pregnant before menses resumes.[2] The need for effective contraception increases if a woman is more than 6 months postpartum, if she supplements her milk with formula, if there is a 6-hour or greater gap between nursing times, and/or if menses has resumed.[151] The average length of postpartum amenorrhea in lactating women is 7 months, and nearly all ovulate by 1 year after delivery.[150]

Coitus Interruptus

Withdrawing the penis from the vagina prior to ejaculation is an ancient technique known by various names such as coitus interruptus, strategic withdrawal, withdrawal method, the sin of Onan (Gen. 38:8-9), and the French method.[2,9,152] It is popular and represents a major male contraceptive technique.[152] However, it should not be used because high pregnancy rates usually result.[18,19,35] A great deal of self-control is necessary to overcome the natural male urge for deeper penile penetration prior to ejaculation. Most young males do not have this control. Large numbers of sperm also can be found in the first part of the ejaculate and even in preejaculate fluid. Other variations such as coitus reservatus where intercourse is sustained for so long that detumescence occurs without ejaculation and coitus obstructivus where pressure is placed on the penis during the male's climax to cause retrograde ejaculation are not recommended.[110] Males who wish to contribute to contraception must rely on abstinence and/or condoms. Although a male contraceptive pill is desirable, it is not yet available. A pill derived from cottonseed and called gossypol has been developed in China,[2,110] but unfortunately, it can cause hypokalemia and irreversible sterility.

Postcoital Douche

Douching has been used for centuries to prevent pregnancy.[9] However, it is associated with a high pregnancy rate.[142] Studies have found that motile sperm can reach the cervical mucus in 90 seconds and the fallopian tubes in 5 minutes.[2] Although douching can be part of normal hygiene, it is not a contraceptive

method. Douching with carbonated beverages is popular but dangerous, sometimes resulting in death.[110]

Noncoital Sexuality

This includes holding hands, petting, kissing, masturbation, and anogenital sex.[9,35] Recommending that teenagers avoid coital activity should not ignore the inevitable phases of adolescent sexuality. These can be important substitutions for coitus.

Abortion

Although many teenagers use abortion as a contraceptive method, it should be stressed that this is not an acceptable method.[153,154] More than 400,000 abortions occur every year to teenagers in this country, and many could be avoided with the use of effective contraception. In general, legal abortions are safe.[155]

Sterilization

Various methods of sterilization are available to both adult males and females.[124,156] However, it is very difficult to sterilize any adolescent because of legal and ethical considerations.[157] Even the sterilization of retarded girls is difficult.[18,158] Usually, it is best to provide effective medical contraception rather than seek sterilization.

Newer Contraceptive Methods

Table 18-23 lists some contraceptive techniques currently under study that may be available in the 1980s and applicable to adolescents.[2,9] It is difficult to know now which ones are or will be appropriate for young people. Side effects may prevent their use. For example, testosterone analogs may be effective in males, but are not favored because of their intramuscular method of administration and complications such as loss of libido, hypertension, increased blood lipids, and liver tumors. Another proposed method is to inhibit FSH and therefore spermatogenesis but not to interfere with LH which affects the libido. Neither analogs of GnRH nor safe chemicals that inhibit epididymal function are a reality for teenagers. Immunization against pregnancy is an interesting idea for both males and females, but numerous immunologic cross-reaction possibilities must be researched carefully before this is feasible.[159] A prostaglandin-releasing tampon is available and currently used as an intermittent abortive agent in some women. In addition, vehicles that cause a slow release of progestin, with or without estrogen, are being investigated.[141] Improved spermicides currently are being developed.[119] Thus, the possibilities for the future are numerous.

Table 18-23. Newer Contraceptive Methods.

A. Male contraceptive methods
   1. Inhibin (FSH suppression)
   2. Epididymal function inhibition
   3. Combination of androgen and estrogen
   4. Analog of testosterone
   5. Immunization
   6. Gossypol (male pill developed in China)
B. Female contraceptive methods
   1. Postcoital contraceptives designed for regular use (Table 18-21)
   2. Prostaglandin-impregnanted tampon
   3. Vaccine to prevent pregnancy, which acts on a beta-subunit of HCG or human placental lactogen
   4. Various vehicles for slow release or progesterone
      a. Newer progestin-IUDs
      b. Subdermal progestin implants (including bracelets)
      c. Intravaginal ring (with or withour estrogen)
      d. Miscellaneous long-acting injectable contraceptives
   5. Improved vaginal contraceptives

Summary

It is the tenet of this chapter that there are many contraceptive techniques available to the adolescent who can be motivated to avoid unwanted pregnancy. No method is ideal for all teenagers, and the clinician can help the young patient choose the method that best meets her needs. Although abstinence and barrier methods can be suggested, the combined oral contraceptive seems to be most popular among youths. The pill is both safe and effective for screened and well-motivated teens. However, thorough knowledge of the birth control pill's absolute and relative contraindications is essential to maximize its

effectiveness and safety (Table 18-8). Careful follow-up also is imperative. In general, a birth control pill is recommended with 30–35 μg ethinyl estradiol and 0.15–1.5 mg progestin (norgestrel, levonorgestrel, or norethindrone).

The safety and efficacy of contraceptive methods prescribed for a teenager must be constantly evaluated because she is at the beginning of her reproductive years. Therefore, methods with specific danger to reproductive potential must be recommended only with extreme caution. Any method chosen by the youth can be immediately changed as her life changes.[137] We can and should help her choose and reevaluate her previous decisions.

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Hematologic Disorders 19

Salvatore Bertolone

The many physiologic changes of adolescence can be associated with nutritional deficiencies that result in hematologic problems.[1] At the same time that rapid weight gain and increased skeletal muscle mass require an increased red blood cell mass, poor diet and menarche contribute to red blood cell loss Iron deficiency continues to be the most common nutritional deficiency in the United States. In some studies, 60% of infants under 2 years and 25% of adolescents were iron deficient.[2] This chapter will focus specifically on iron deficiency anemia and some of the coagulation disorders that may present during adolescence. A list of selected readings is provided for an in-depth understanding of all the hematologic changes that may take place during this critical period.

Classification of Anemias

Anemia is a reduction in red blood cell (RBC) mass or blood hemoglobin concentration. The designation at various ages of normal values for hemoglobin and hematocrit has a profound influence on the estimation of nutritional anemias' prevalence.

Table 19-1 shows the hemoglobin/hematocrit levels, with the lower limits of normal at sea level. The limit for differentiating the anemic from the normal patient is two standard deviations below the mean of a normal population. By definition, this results in 2.5% of the normal population being classified as anemic. Conversely, the values for those who are hemoglobin deficient will be distributed in such a way that some persons will be within the normal range when, in fact, iron therapy would raise their hemoglobin. The values in Table 19-1 are for a reference population of white children. Black children may average 0.5 g/dl less in hemoglobin values.

Absolute anemia with a decreased RBC mass can be classified according to morphologic criteria. Although not a completely suitable classification, its main advantages are that it emphasizes the importance of direct microscopic observation of red cells and forces the physician to consider the most important types of treatable anemia. This morphologic indices classification subdivides anemia accordingly into macrocytic anemia (MCV, 97–160 μ^3), normocytic anemia (MCV, 80–96 μ^3), and microcytic hypochromic anemia (MCV, 50–79 μ^3).

The adolescent female between 12 and 14 normally should have a hemoglobin of approximately 13.5 g/dl, with 12 the lower limit of normal. The 15- to 17-year-old girl should have a hemoglobin of approximately 14 g/dl, also with 12 the lower limit of normal. The mean corpuscular volume (MCV) of red blood cells has a mean of approximately 86 fl, with the lower limit of normal being 78 (Table 19-1). The increased use of electronic Coulter counters that directly measure the mean corpuscular volume has aided in determining normal values and norm variance. The Coulter counter's use of the MCV determination takes into account the normal developmental changes—particularly during adoles-

Table 19-1. Normal Mean and Lower Limits of Normal for Hemoglobin, Hematocrit, and MCV Determinations.

Age (Years)	Hemoglobin (g/dl)		Hematocrit (%)		MCV (fl)	
	Mean	Lower Limit	Mean	Lower Limit	Mean	Lower Limit
0.5–1.9	12.5	11.0	37	33	77	70
2–4	12.5	11.0	38	34	79	73
5–9	13.0	11.5	39	35	81	75
8–11	13.5	12.0	40	36	83	76
12–14						
Female	13.5	12.0	41	36	85	78
Male	14.0	12.5	43	37	84	77
15–17						
Female	14.0	12.0	41	36	87	79
Male	15.0	13.0	46	38	86	78
18–49						
Female	14.0	12.0	42	36	90	80
Male	16.0	14.0	47	41	90	80

Lower limits of normal derived from estimated mean minus 2 S.D. From Sallman PR, Siimes MA: Journal of Pediatrics 94:26, 1979.

cence—in RBC size. The most prevalent anemia in childhood and adolescence is associated with a low MCV. The two conditions most likely to cause a low MCV are iron deficiency and thalassemia minor.

Macrocytic anemias include vitamin B_{12} and folate deficiencies. Although vitamin B_{12} deficiency is a rare cause of anemia in children and adolescents, it is an important one because of the danger of irreversible neurologic damage if not diagnosed and treated early. Most cases of vitamin B_{12} and folate deficiency involve an absorption defect. A deficiency in dietary intake is rare, but can occur particularly in adolescents with inflammatory bowel disease. Both folate and vitamin B_{12} absorption are decreased in adolescents on anticonvulsive therapy. Other causes of macrocytic RBCs include reticulo cytosis, liver disease, hypothyroidism, and Down's syndrome. Table 19-2 lists a summary of red blood cell indices and the common conditions associated with changes in RBC size.

Table 19-2. Morphologic Classification of Anemias and Clinical Associations.

Types of Anemia	Red Blood Cell MCV (μm^3)	Causes
Macrocytic	97–160	Reticulocytosis
		Vitamin B_{12} deficiency
		Folic acid deficiency
		Liver disease
		Hypothyroidism
		Dysserythropoietic anemias
		Down's syndrome
Normocytic	80–96	Congenital hemoglobinopathies
		RBC enzyme deficiencies
		Coomb's and hemolytic anemias
		Chronic renal disease, usually
Microcytic hypochromic	50–79	Iron deficiency
		Thalassemia
		Lead
		Chronic inflammation
		Sideroblastic anemias

Iron Deficiency

Iron deficiency is believed to be the most common nutritional disturbance in infants, children, and adolescents in the United States. Since the turn of the century when iron deficiency was first recognized as the cause of anemia, its prevalence has not changed dramatically. Both iron deficiency and iron deficiency anemia occur with increasing frequency in adolescents, particularly in girls, who have an incidence of between 10 and 27%.[1] Iron primarily is needed during growth for the expansion of blood volume and muscle mass. Because this expansion is so rapid in adolescents, it is no wonder that there is such a high incidence of iron deficiency and iron deficiency anemia.

Iron deficiency development proceeds in a series of overlapping steps. Iron deficiency is a state where the content of iron in the body is below normal. The term "iron depletion" has been applied to an earlier stage of iron deficiency where storage iron is decreased or absent, but serum iron concentrations and blood hemoglobin and hematocrit levels are normal. The initial depletion of storage iron is followed by a fall in iron saturation of serum transferrin. This ultimately results in what is recognized as anemia, a decreased net production of red blood cells and a drop in hemoglobin.[3].

The time-honored method for assessing storage iron was to do a bone marrow aspiration and measure the stainable iron in the marrow aspirate. Currently, the measurement of serum ferritin is thought to be a reliable indicator of decreased marrow iron stores.[4] Iron in excess of that required to form hemoglobin is stored in tissues as ferritin, a soluble protein specifically available for this function. Ferritin normally is in the serum but in very small quantities (10–200 ng/ml).[5,6] The quantity of storage iron and the concentration of serum ferritin correlate in most conditions. A low concentration of serum ferritin is characteristic of iron deficiency only. High levels can be found in those with iron overload as a result of thalassemia and sickle cell anemia. In certain diseases, including chronic inflammatory disease, infection, liver disease, and malignancy, concentrations may be elevated out of proportion to storage iron because serum ferritin is an acute phase reactant.[7]

The second stage in the development of iron deficiency anemia comes after the storage iron is depleted. During this period, a drop in the serum iron and total iron-binding capacity occurs. Serum iron concentrations in adolescents normally range from 110 to 120 μg/dl. In both adults and adolescents, a transferrin saturation of 16% is considered the lower limit of normal.[8] There are large biologic variations in serum iron concentrations that result in many false-positive and -negative diagnoses. Serum iron concentrations may show marked unexplained fluctuations as well as diurnal variation. Thus, serum iron levels should never be drawn after 10 a.m. or when a patient has received iron therapy by mouth in the past 3 days.[9] During this second stage of iron-deficient erythropoiesis, the erythroid iron supply is diminished, but the circulating hemoglobin is not significantly decreased.

The third and final stage is overt iron deficiency anemia. Red blood cell indices are intermediate between measurements of iron-deficient erythropoiesis and frank iron deficiency anemia. Hypochromic and microcytic RBCs will appear in the circulation before a significant decrease in hemoglobin concentration. The mean corpuscular volume is regarded by many as the most sensitive indicator of small red blood cell size.[10] In adults, a moderate decrease to 70 to 80 fl often is seen in those with anemia of chronic disease or malignancy. Values below 70 fl occur only with iron deficiency anemia or thalassemia minor. In geographic areas where thalassemia rarely is seen, an MCV below 70 is strong evidence of iron deficiency anemia. Causes of microcytic hypochromic red blood cells include iron deficiency, thalassemia, lead poisoning, chronic infection, severe protein or copper deficiencies, and sideroblastic states.

Clinical Manifestations of Iron Deficiency

Because hemoglobin accounts for approximately two-thirds of the iron in the body, it comes as no surprise that the evaluation of iron deficiency has always emphasized anemia. It is therefore natural to think of manifestations of iron deficiency as decreased con-

centrations of hemoglobin. However, recently it has been possible to delineate some of the effects of iron deficiency on cells other than erythrocytes and on tissues other than blood.

Iron deficiency may involve impaired cellular immunity, intestinal function, epithelium, and body growth. At the cellular level, the results of a lack of iron include deficiencies of the cytochrome oxidase system; decreased activity of catalase, glutathione, peroxidase, and succinate dehydrogenase; and disturbances in DNA synthesis.[11,12] Infants and adolescents with severe iron deficiency usually are more irritable, have poor weight gain, atrophy of the papillae of the tongue, pagophagia, and alterations in small bowel mucosal function.

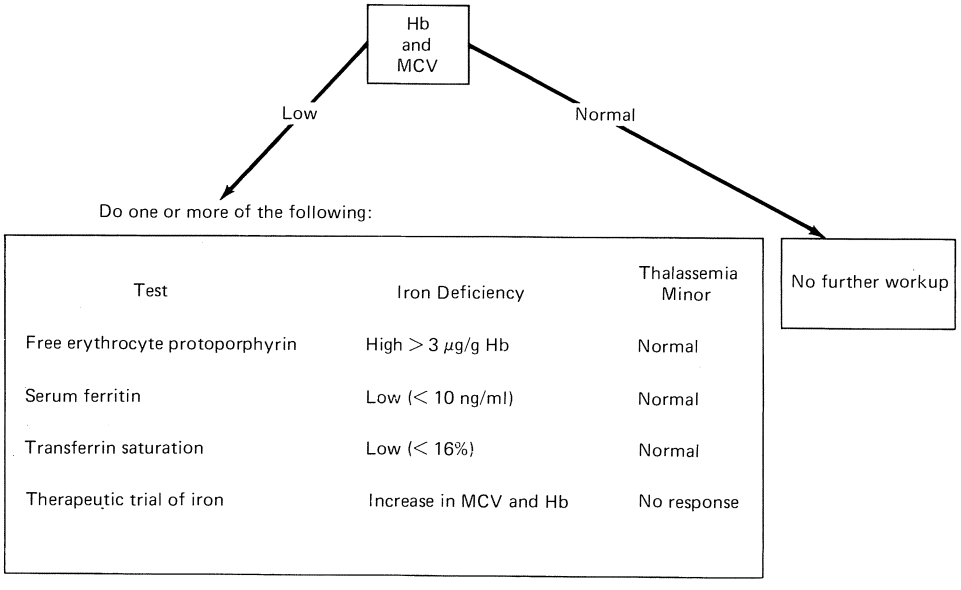
Despite the complexities of designing an experiment and difficulties in interpreting the data, evidence strongly supports the theory that mental performance is impaired by iron deficiency.[13] These studies suggest that iron-deficient children score lower in intelligence tests and have decreased attentiveness, restricted perception, and impaired performance in measurements of latency and associated reactions. In the classroom, some adolescents with presumed iron deficiency are seen as more destructive, irritable, and restless.[14] Further work, however, is necessary to confirm some of these observations.

Diagnosis of Iron Deficiency

A good history and physical examination for those at significant risk is the most cost-effective approach when low hemoglobin is suspected. A decreased hemoglobin concentration in association with microcytosis strongly suggests iron deficiency. The diagnosis may be confirmed by a reduced serum ferritin and/or a reduced serum iron concentration and percent saturation. In the absence of findings in the history and physical that suggest another etiology (e.g., chronic blood loss), the clinician can simply examine a peripheral smear, observe low MCV with microcytosis, and start a therapeutic trial of ferrous sulfate. Figure 19-1 gives an orderly algorithm for the screening of anemia based on hemoglobin level and MCV values.

Treatment of Iron Deficiency

Except under the most unusual circumstances, oral therapy is preferred for the treatment of iron deficiency. The treatment of choice for almost all causes of iron deficiency is oral doses of ferrous sulfate. This iron salt is the standard against which the efficacy of a



Test	Iron Deficiency	Thalassemia Minor
Free erythrocyte protoporphyrin	High > 3 μg/g Hb	Normal
Serum ferritin	Low (< 10 ng/ml)	Normal
Transferrin saturation	Low (< 16%)	Normal
Therapeutic trial of iron	Increase in MCV and Hb	No response

Figure 19-1. Iron deficiency and related nutritional anemias.

multitude of other compounds is measured. It is both inexpensive and well tolerated.

Claims that more expensive salts or their derivatives provide better absorption or fewer gastrointestinal side effects have been questioned, with recent studies failing to show any distinct advantage over ferrous sulfate.[15] The dose of oral iron is based upon the amount that is adequate for maximum hematologic response. The adult dosage with the least side effects is about 3 mg/kg per day of elemental iron in the form of ferrous sulfate divided into one dose at breakfast and one at dinner.[16] Administration between meals further increases the percentage of absorption.

If intolerance to oral iron salts occurs, the dose can be either reduced or taken with meals. The recommended dose, assuming an average bioavailability of 20%, is sufficient to permit a potential daily rise in the hemoglobin level of more than 0.4 g/dl. The rise in hemoglobin that is actually observed in any particular patient depends on the initial level of hemoglobin and the duration of the observation. The lower the hemoglobin concentration, the greater the daily rise, while the shorter the observation period, the greater the calculated hemoglobin rise each day. If the initial hemoglobin value is low, the rise in hemoglobin may start at 0.3 g/dl or more for the first week of treatment, then gradually fall off to 0.15 g/dl or less. A reticulocytosis may be observed 2 or 3 days after the onset of treatment, peaking at about 7 to 10 days. Anemia and microcytosis are corrected after 3 or 4 months of therapy. To avoid iron overloading, therapy should not extend beyond 1 or 2 months after anemia is reversed. This is sufficient to reconstitute depleted iron stores.[17] Oral iron preparations at the recommended doses usually turn the stools black, so the patient must be warned that this is not abnormal. Some adolescents complain of vomiting, diarrhea, constipation, and/or abdominal discomfort. If this occurs, the patient should stop the iron for 24 hours, resuming at one-half the recommended dose and gradually working up to the full amount.

A variety of dietary factors influences the amount of iron, including medicinal iron, that may be absorbed from any source. Medicinal iron is maximally absorbed when given to a person who is fasting. However, we prefer to give iron with meals. Under these circumstances, iron absorption varies. Iron with meals may result in an approximately 50% decrease in absorption.[18] Meats more so than other food enhance the absorption of nonheme iron. Veal, pork, lamb, liver, chicken, and fish are roughly equal in their ability to enhance absorption. Products such as eggs, milk, or cheese have an inhibitory effect. Meals with high fiber content, such as bran and whole wheat breads, also significantly inhibit the absorption of ferrous sulfate.[19] Coffee and tea inhibit iron absorption; tea has been shown to inhibit iron absorption by 75%.[20] The administration of ferrous sulfate with antacids or tetracyclines also will decrease iron absorption.[21]

Although it usually is not necessary, the bioavailability of iron medications may be increased by simultaneously taking large quantities of vitamin C.[22] Ascorbic acid increases iron absorption by maintaining iron in a reduced and more soluble form. Because many people treat themselves with vitamin C, the relationship between iron absorption and the vitamin has become more important. Some believe that fortifying food with ascorbic acid may be more effective than iron in improving nutrition in countries with a high incidence of iron deficiency.

Various iron preparations have been used for the parenteral treatment of iron deficiency. Iron is bound to a substrate that stabilizes it in the form of a complex. Substances such as sucrose and modified dextran have been used as stabilizers. These iron preparations are of high molecular weight. Recently, a low molecular weight complex of iron, sorbitol, and gluconic acid has been investigated. Iron dextran (Imferon) still remains the most widely used in this country. This product contains 50 mg/ml of elemental iron. The calculation for the volume of required iron dextran is based on an average blood volume of 75 ml/kg, the requirement of 50% more iron for the replenishment of iron stores, and the fact that 1 g of hemoglobin contains 3.5 mg of iron.[23]

ml of iron dextran =
weight (kg) × 0.076 × desired rise in hemoglobin (g/dl) (HgD-HgO)

The total dose of iron dextran usually is distributed over two or three daily injections. Intramuscular injections are painful, the skin becomes discolored, and care must be taken to avoid back flow into subcutaneous tissue. Moreover, the therapeutic response is not significantly better than with oral medication. Severe side effects include severe anaphylactic reactions, staining of the skin at the injection site, asthma, vomiting, chills, fever, arthralgia, and urticaria.[24]

Iron deficiency anemia occasionally is not corrected by oral iron. Table 19-3 lists the causes of iron refractory anemia. Some of these anemias, because of poor iron utilization, also would be expected not to respond to parenteral therapy. Failure to comply is the leading cause of this problem. Thus, the first step is to determine if the adolescent is taking the iron medication; this can be verified by a simple 2-minute stool examination. When a small amount of stool is mixed with 2 N hydrochloric acid and placed on filter paper, one drop of 0.25% potassium ferricyanide will turn it a bluish color (ferrous ferricyanide) if the child has been taking medicinal iron. The test could be made positive by gastrointestinal bleeding, which should be excluded by a stool guaiac test.

Coagulopathies

Hereditary deficiencies of all plasma hemostatic factors have been recognized and diagnosed. The most common inherited coagulation disorders usually are the hemophilias and include deficiencies of factors VIII, IX, and XI. Because factors VIII and IX are linked, they become important only in genetic counseling.

Table 19-3. Causes of Iron Refractory Anemia.

1. Wrong diagnosis
2. Lack of compliance
3. Improper dosage administration
4. Poor utilization (chronic diseases)
5. Malabsorption syndromes
6. Chronic low grade blood loss

Hemophilia

Factor XI deficiency is an autosomal recessive form of bleeding disorder, which is the least common of the hemophilia bleeding disorders and found mainly in persons of Jewish ancestry. The prothrombin time will be normal and the activated partial thromboplastin time abnormal. Assay for factor XI will confirm a low level of coagulant activity.

Von Willebrand's Disease

Von Willebrand's disease is the most common coagulopathy the physician treating the adolescent girl is likely to encounter. This relatively common hereditary bleeding disorder was first described about 50 years ago by Eric von Willebrand. It can be inherited in an autosomal dominant or recessive form.[25,26] The most common form of the disease occurs with relatively mild bleeding. It is not uncommon for a female to go undiagnosed until menarche. Although von Willebrand's disease can be suspected based on a history of bleeding, confirmation requires a combination of laboratory tests.

There is no substitute for a good history and physical examination. Nosebleeds and easy bruising are the most common symptoms in children and young adults with coagulopathies. Bleeding may occur after dental extractions, lacerations, or fractures. A girl may develop menorrhagia with menarche. A family history of bleeding often is the most important diagnostic clue.

Von Willebrand's disease is a lifelong bleeding disorder that is characterized by prolonged bleeding and a decreased level of factor VIII. Recent studies have identified families with similar but not identical disorders, which suggests that von Willebrand's disease would be more appropriately called a syndrome. There are currently at least five variants of von Willebrand's disease. The disease has both a prolonged bleeding time (abnormal platelet function) and decreased levels of factor VIII coagulant activity. The factor VIII abnormality in von Willebrand's disease is somewhat more complex than that of straightforward factor VIII hemophilia.[27,28]

Several studies have shown that platelets from patients with von Willebrand's disease do not function normally in a variety of in vitro tests. Not only may the bleeding time be abnormal, but so may platelet aggregation studies. In normal subjects, ristocetin causes platelet aggregation when added to citrated platelet-rich plasma. However, there is no aggregation when the platelet-rich plasma of those with severe von Willebrand's disease is tested. Although platelet function is abnormal, the abnormality does not appear to be intrinsic to the platelet because all the hemostatic and platelet defects in von Willebrand's disease can be corrected by plasma fractions containing factor VIII.[29–31]

Current evidence suggests that factor VIII (antihemophiliac factor), in addition to correcting the coagulation defect in hemophilia (factor VIII AHF), also is necessary both for proper platelet function and in certain in vitro tests such as platelet retention and ristocetin-induced aggregation. Patients with von Willebrand's disease are lacking in this platelet property of factor VIII and factor VIII AHF. An assay for this property of factor VIII in plasma has been developed. Because a deficiency of this activity is relatively specific to von Willebrand's disease, it is called the von Willebrand factor (VWF factor, factor VIII VWF, or ristocetin cofactor). Some postulate that the von Willebrand's factor and the factor needed for a normal bleeding time are one and the same.[32]

Patients with von Willebrand's disease usually show concordant decreases in levels of antihemophilaic factor (factor VIII AHF), von Willebrand's factor (factor VIII VWF), and factor VIII antigen (factor VIII AGN). In contrast, only factor VIII AHF is decreased in hemophilia. The nature of the factor VIII abnormalities in these two disorders has not been defined. Table 19-4 summarizes the laboratory tests and coagulopathies.

Clinical Features

Symptoms usually occur early in childhood and may mysteriously decrease with age. Although bleeding that results in death is unusual, it can occur. The most common bleeding includes mucosal and cutaneous hemorrhages, with epistaxis and easy bruising among the most frequent symptoms. Hemarthroses are rather infrequent and usually related to trauma.[33] Most patients with mild laboratory abnormalities may be asymptomatic.

Menorrhagia has been reported in 55% of women with von Willebrand's disease.[34,35] Excessive postpartum bleeding was reported in eight of 22 women. This may be related to elevated factor VIII AHF levels during pregnancy.

Diagnosis is based on a strong family history, a prolonged bleeding time, and measurement of factor VIII AHF activity and factor VIII von Willebrand's factor (ristocetin cofactor). Both factor VIII AHF and bleeding time abnormalities may show wide fluctuations when the patient is repeatedly tested. In classic hemophilia, factor VIII AHF is very low and factor VIII AGN is low normal, whereas in von Willebrand's disease factor VIII AHF may be low normal, factor VIII antigen normal, and factor VIII VWF markedly low. A prolonged bleeding time and decreased factor VIII AHF with a low ristocetin cofactor usually establish the diagnosis. A prolonged bleeding time may be the result of aspirin, aspirin-containing compounds, and/or certain cough medicines and antihistamines. The activated partial thromboplastin time may be prolonged or borderline-prolonged, but the prothrombin time always is normal. Therapy is directed toward increasing the level of factor VIII coagulant activity and shortening the bleeding time. Factor VIII coagulant activity may be increased by using cryoprecipitate or fractions rich in factor VIII AHF. Correction of the bleeding time is more variable.

Thrombocytopenia

Another significant cause of bleeding and bleeding abnormalities in the adolescent female is thrombocytopenia. The platelet or thrombocyte is the smallest circulating cellular element in the blood, its chief function being in primary hemostasis. Platelets interact with blood vessel and coagulation proteins to form a mechanical seal that prevents blood from leaving the intravascular spaces.

A normal platelet count should be greater than 150,000 platelets/mm^3. Bruising and

Table 19-4. Laboratory Tests.

Disease	Screening			Specialized Assays			
	Bleeding Time	Prothrombin Time	Partial Thromboplastin Time	Platelet Aggregation (Ristocetin)	VIII AHF	VIII VWF	VIII AGN
Factor VIII deficiency: hemophilia A	N	N	ABNL	N	ABNL	N	N
Von Willebrand's disease (typical)	ABNL	N	+/−	ABNL	ABNL	ABNL	ABNL
Factor IX: deficiency hemophilia B	N	N	ABNL				
Factor II, V, VII, X deficiency	N	ABNL	+/−				
Factor XI deficiency	N	N	ABNL				

N, normal; ABNL, abnormal; +/−, variable.

thrombocytopenia are not evident until the platelet count drops below 75,000 to 100,000 platelets/mm^3. The classic symptoms of the thrombocytopenic state include spontaneous bleeding into the skin or mucous membranes and formation of either small pinpoint hemorrhages (petechiae) or larger superficial ecchymoses. The differential diagnosis of petechiae and/or bruising would include nonthrombocytopenic states and vascular disorders such as Henoch-Schönlein purpura as well as qualitative platelet disorders.

Baseline laboratory evaluation of the adolescent with petechial or purpuric hemorrhage should include a complete blood count, platelet count, and peripheral blood smear. The complete blood count may suggest an underlying cause of the thrombocytopenia. The size of the platelets may establish whether they are young or old. This should be done to exclude other diseases, suggested by the history and physical exam that may predispose the girl to thrombocytopenia.

Autoimmune thrombocytopenic purpura is most frequent in young children between ages 2 and 6. The adolescent female may predominate with a 3:1 ratio in the second decade.[36] Although originally called idiopathic thrombocytopenic purpura, there is ample evidence to document its immune-mediated nature, and it is now referred to as autoimmune thrombocytopenic purpura.[37] Resulting from an excessive destruction of circulating platelets, the more common acute form accounts for 85–90% of all cases.[38] Whereas the acute form is spontaneous and permanent recovery occurs within 6 months, the chronic form—10% of all cases—is more insidious, persisting for many months, and occuring more often in adolescent females. A history of an antecedent febrile illness has been reported in up to 85% of these cases. All of the usual childhood illnesses and immunizations also have been associated with this disease.

The course of autoimmune thrombocytopenic purpura varies, and the clinician cannot predict whether a child will have the more common acute self-limiting form or chronic disease. These facts fuel the controversy over therapeutic approach. Acute autoimmune thrombocytopenic purpura requires supportive care only. However, there are some authors who suggest that early intervention with steroids may alter the thrombocytopenia associated with the acute course.[39] There is no evidence that steroids are related to a change in the chronic course of thrombocytopenic purpura.[40] If used, cortico-steroids (Prednisone) are given at 2 mg/kg/day for 2–4 weeks and then tapered off. Splenectomy also should be considered for those who have had persistent hemorrhagic symptoms for approximately 1 year and have not responded to corticosteroids. Other entities to be ruled out in the differential diagnosis of acute or chronic autoimmune thrombocytopenic purpura include Epstein-Barr virus disease, cytomegalovirus, collagen-vascular disorders, and marrow storage diseases such as the leukemias.

The adolescent female has menarche at a time when her eating habits are probably the

worst they will ever be. The increased blood loss from menstrual periods coupled with decreased iron intake puts her at extreme risk of developing iron deficiency and iron deficiency anemia. She also is at risk for the common acute viral and marrow replacement disorders such as leukemia, which can lead to thrombocytopenia in an otherwise healthy person. A higher incidence of collagen-vascular disorders in adolescents as well as inflammatory bowel disease also emphasizes the increased risk of hematologic problems in the adolescent. The practitioner should never rule out a congenital bleeding disorder because it has not been diagnosed until the second decade of life. The symptoms and complaints of increased bruisability and/or increased gum bleeding may only become apparent with the onset of menarche and menorrhagia. The key to recognizing any hematologic changes in the adolescent is a good history and physical examination.

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Drug and Alcohol Abuse 20

G. Randolph Schrodt, Jr. and Kenneth N. Schikler

Physicians who treat adolescents invariably face cases of substance use and abuse. In the past 20 years the use of psychoactive chemicals has become an accepted and, in a statistical sense, even a "normal" part of adolescence and young adulthood. Regardless of the physician's attitude about drug use and despite shifting legislative responses, the majority of youth today by the time they become adults will have had experience with alcohol, tobacco, caffeine, and marijuana.[1] A significant proportion of adolescents regularly use drugs such as hallucinogens, amphetamines, cocaine, sedative-hypnotics, opiates, and inhalants.

Recent large-scale epidemiologic studies focus on the problem.[2] As with adults, alcohol is the most common drug used and abused by teenagers. A 1981 survey of high school seniors reported that 93% had previously used alcohol and more than two-thirds within the past month.[1] A national survey of 10th to 12th grade students classified 38% of boys and 26% of girls as problem drinkers.[3] Other studies suggest that the sexes are progressing toward parity in their drinking habits.[4]

Marijuana use has increased dramatically. From 1962 to 1979, the percentage of 18- to 25-year-olds who reported they had "ever tried" marijuana rose from 4 to 68%.[5] Although the trend toward daily or regular use may be leveling off, teenagers tend to use drugs at an earlier age.[1]

While other drugs are used less frequently, the 1981 national cohort study of high school seniors reported that 32% had used stimulants, 17% inhalants, 17% cocaine, 16% sedatives, 16% hallucinogens, 15% tranquilizers, 10% opiates, and 1% heroin.[1]

Definitions

Every adolescent who uses or has tried psychoactive substances does not necessarily have serious psychopathology or drug problems. Likewise, certain patterns of drug use do not invariably present serious physical or psychologic health risks. The reason scare tactics do not deter adolescents from using drugs may be because they can observe many of their peers using drugs without any serious consequences. In fact, teenagers appear particularly astute at diagnosing which of their peers have drug problems.

How then can we clinically define substance abuse? The American Psychiatric Association in developing diagnostic criteria for substance abuse disorders for the Diagnostic and Statistical Manual of Mental Disorders—III (DSM-III) has focused on three major parameters to distinguish substance "abuse" from "nonpathological substance use for recreational or medical purposes."[6]

The first discrimination focuses on a pattern of pathologic use.

> "Depending upon the substance, this may be manifested by intoxication throughout the day, inability to cut down or stop use, repeated efforts to control use through periods of temporary abstinence or restriction of use to certain times of the day,

> continuation of substance use despite a serious physical disorder that the individual knows is exacerbated by use of the substance, need for daily use of the substance for adequate functioning, and episodes of complications from substance intoxication (e.g., alcoholic blackouts, opioid overdose).[6]"

The teenage drug abuser demonstrates a distinctive pattern in attempting to cope with the developmental problems of adolescence through the use of psychotropic substances, the result of which is that the drugs become a major complication in themselves.

The second criterion of DSM-III substance use disorders is "impairment in social or occupational functioning caused by the pattern of pathological use."[6] The psychosocial context of adolescence influences the specific problem areas and includes difficulties with family, friends, academics, heterosexual relations, legal authorities, and personality development.

The third criterion concerns the duration of pathologic drug use. Specifically, the use of drugs must be sufficiently frequent if they are to be linked to the adolescent's difficulties in functioning. DSM-III suggests a minimum drug use duration of 1 month.[6] However, this is often a difficult clinical judgment because the sequence of difficulty in functioning and substance use is not always clear from the history. This is confounded by the association of other types of psychopathology (associated with disturbances in emotions, cognition, behavior, and development) with substance use disorders.

Substance abuse can have a medical impact at any stage whether during acute intoxication, chronic use, abstinence after chronic use, or socially related activities that are closely linked to the use of either licit or illicit chemicals.

Psychoactive substances vary substantially in pharmacologic potency, activity, and mode of administration. Physical and/or psychologic dependence varies according to the substance.

Physical dependence occurs with regular and substantial use of agents such as sedative-hypnotics and opiates. It is associated with the development of "tolerance," seen clinically as the need for a progressively increasing dose to provide the same pharmacologic effect, and "abstinence" or withdrawal symptoms upon abrupt discontinuation. Such abstinence symptoms range from mild discomfort and somatic symptoms (as with nicotine withdrawal) to potentially life-threatening conditions such as delirium tremens and withdrawal from other sedative-hypnotics.

Psychologic dependence generally also occurs with substance abuse. Psychologic dependence corresponds to the pleasant and satisfying psychic effects of drug intoxication. These subjective effects provide reinforcement for the repetitive and compulsive use of drugs. Psychologic dependence is reflected in behaviors such as incessant drug seeking and hoarding.

Biopsychosocial Aspects of Substance Abuse

The etiology of adolescent substance abuse is multifactorial. To understand the teenage drug abuser one must have an appreciation of the dynamics of adolescent development.

Rapid biologic, psychologic, and social adaptations are required during adolescence. Traditionally, it has been considered a time of turmoil. Recent research suggests, however, that turmoil is not necessary nor, in fact, the norm of adolescent development.[7] Nevertheless, significant challenges face the teenager during the trial period of adulthood.

The adolescent's rapid growth and sexual maturation contribute to a changing self-image and heightened body focus. Such changes often are perceived as mysterious and threatening and disturb narcissistic equilibrium. It is typical for adolescents to be critical of themselves. The emergence of sexuality and sexual experimentation often provokes particularly intense anxiety.

Teenagers who fail to deal successfully with these physical changes or who must adapt to physical or mental handicaps may turn to mind-altering substances as a way of alleviating anger, depression, or anxiety. In general, psychotropic substances can impair sexual performance and libido and actually magnify anxiety regarding sexual adequacy.

Other biologic and genetic factors are significant in the predisposition to substance

abuse. The teenage sons of alcoholics have distinctive electroencephalograph (EEG) patterns after drinking alcohol that differ from other teenager's responses.[8] Adoption and twin studies also support the role of heredity in alcoholism.[9] Other studies show significant differences between alcoholics and nonalcoholics in the metabolism of alcohol.[10]

Profound psychologic changes occur during adolescence in response to biologic maturation. The establishment of a personal identity—that sense of wholeness and cohesiveness of self in relation to the world—is the essential developmental task.[11] Impaired personal identity commonly is associated with pathologic substance use. Although there is no well-defined addiction-prone personality, the adolescent alcoholic frequently is noted to have a sense of inadequacy, low frustration tolerance, poor problem-solving skills, and generally unrewarding interpersonal relationships.[12] These problems in personality development often lead to the use of drugs as a way to cope, which in turn contributes to further failure in psychologic growth.

Coexisting psychiatric illness and substance abuse commonly is seen. Attention deficit disorder (hyperactive syndrome, minimal brain dysfunction) is characterized by short attention span, problems of information processing, and impulsive behavior. Abuse of drugs, especially alcohol and marijuana, frequently is seen in this population. Compulsive drug use also is considered a symptom of masked depression in adolescents, and treatment must be directed toward the primary affective disorder.[13]

Psychologic development is accompanied by revolutionary changes in the social arena. The formation of personal identity requires a separation from the family and a distancing from the security and protection of the family environment. The influence of peers as models of identification and standard bearers of values and norms reaches a degree not seen before. Studies have shown that the use of drugs by a teenager's best friend is the most common reason for trying drugs (although not necessarily in regular or pathologic use).[14]

Adolescents who do not have supportive parents or sufficient control are prone to substance abuse. Perhaps the most significant risk factor for abuse, particularly alcohol abuse, is a parent or relative who drinks too much. Although genetic transmission of a predisposition to substance abuse may be a factor, also significant are the effects of role modeling and family dynamics. A social milieu that encourages and supports the use of alcohol and other drugs often surrounds the teenage substance abuser.

Contemporary culture in many ways reinforces the adolescent's curiosity and experimentation with drugs, which becomes almost a rite of passage into adulthood. Diazepam is consistently one of the most prescribed drugs for adults, and social drinking is an integral part of activities ranging from sporting events to church picnics.

Alcohol

Alcohol is the substance most commonly abused by teenagers. Although alcoholism usually is thought to be a disease of adulthood, most adult alcoholics did in fact begin abusing alcohol early in adolescence. Moreover, adolescents are susceptible to both acute and some chronic medical problems seen in alcoholic adults and are particularly at risk for serious psychologic consequences.

Alcohol is rapidly absorbed from the stomach and upper small bowel and is evenly distributed to all body compartments. Functionally, it is a central nervous system depressant, and its effects are dose dependent. With a low-level dose equivalent to 1 to 2 oz./hour, alcohol causes a pleasant disinhibiting effect on mood, thought, and behavior. At slightly higher doses that produce a 0.1% blood alcohol concentration (legal intoxication), significant psychomotor incoordination occurs, with associated vertical nystagmus, ataxia, dysmetria, and slowed reaction time. Progressively higher doses produce increased somnolence and ultimately stupor, coma, and death.

Regular alcohol use results in the adaptation of body systems (such as an increase in liver metabolic enzymes) which is noted clinically by the development of tolerance. After tolerance has developed, abrupt cessation of alcohol results in a withdrawal syndrome varying in intensity from mild shakes to

delirium tremens, a life-threatening medical emergency. Symptoms progress from nausea, insomnia, tremulousness, and general sympathetic nervous system arousal to disorientation, hallucinations, and grand mal seizures. The alcohol abstinence syndrome requires prompt recognition, and responds to treatment with intramuscular magnesium sulfate or gradual detoxification with a sedative such as chlordiazepoxide.

The medical consequences of alcohol abuse in adolescence extend beyond the direct effects of intoxication and abstinence. Alcohol is implicated in more than half of all fatal automobile accidents, which account for about 35% of adolescent mortality. Many other cases of minor and major trauma are associated with alcohol abuse. Although a sedative, alcohol's disinhibiting effect often results in violent behavior, and in fact, criminal behavior often is associated with alcohol use. In a small segment of the population, minimal amounts of alcohol result in "pathologic intoxication," a syndrome marked by disorientation, impulsive, aggressive behavior, and frequent injury.

Acute overdosage with alcohol may be associated with erosive gastritis, hematemesis, and epigastric pain; acute pancreatitis with acute abdominal pain, hyperamylasemia, and increased lipase activity; or central nervous system depression and coma. Alcohol acts synergistically with other sedative-hypnotics to produce CNS depression, a combination seen commonly in accidental and intentional adolescent overdoses. Alcohol's vasodilatory effects predispose the intoxicated person to significant hypothermic injury, and acute intoxication may be complicated by hypoglycemia. Chronic alcohol use in the adult is associated with neuropsychiatric deteriorative diseases, myocardial disease, alcoholic hepatitis, and cirrhosis. These complications fortunately are rare in teenagers. The hepatocellular effects seem to be secondary to nutritional inadequacies.

Significant elevations in gamma glutamyl transpeptidase (GGTP), a sensitive enzyme found in the hepatobiliary tract and other tissues, are seen in teenage alcohol abusers.[15] Whether elevated GGTPs reflect a significant change in liver function remains to be seen. The effect of adolescent alcoholism on pubertal growth has been studied in rats and has been shown to retard the pubertal growth spurt. However, this effect is reversible with good nutrition.[16]

Psychologic maturation also may be impeded by chronic alcohol use. Impairment of interpersonal relations, particularly sexual relations, is often a direct consequence of alcohol abuse. Decreased sexual interest and performance due to alcohol abuse may heighten sexual anxiety, and the continued use of alcohol stunts the growth of healthy coping skills.

Alcohol abuse during pregnancy presents a number of hazards in addition to the general nutritional and medical problems. Fetal alcohol syndrome (FAS) is found in more than one-third of the offspring of chronic, heavy daily drinkers.[17] FAS is characterized by (1) irreversible prenatal and postnatal growth deficiency, (2) central nervous system dysfunction and mild mental retardation, (3) abnormal facial development with short palpebral fissures and hypoplastic nose and maxilla, and (4) malformations of other organs including cardiac, skeletal, and renal systems.[17] In addition, acute alcohol abuse by the mother may result in CNS and respiratory depression in the neonate.

Sedative-Hypnotics

Sedative-hypnotic or "downer" abuse involves a diverse group of compounds including benzodiazepines (diazepam, chlordiazepoxide), barbiturates, methaqualone (Quāāludes), and glutethimide.

Acute intoxication generally produces a clinical picture similar to that seen with alcohol intoxication, with the exception that the benzodiazepines rarely cause death when taken alone.[18] Cross-tolerance and additive effects with other CNS depressants are seen with all compounds in this group. Physical dependence and an abstinence syndrome similar to that observed in alcohol withdrawal also are seen in the chronic sedative abuser. Onset of abstinence symptoms varies with the compound; the sedative-hypnotic abstinence syndrome is associated with a high mortality rate if untreated.

Sedative-hypnotic withdrawal under medical management should be done with the patient hospitalized. It is important to begin with a pentobarbital tolerance test to determine physiologic tolerance, because it is often difficult to get an accurate history of the amount regularly taken.

Marijuana

Marijuana use accelerated during the 1960s and 1970s and has become a widely accepted social drug in the United States. Its possession and use still are illegal, although in some communities it essentially has been decriminalized. The use of marijuana—especially its medical consequences—has remained a fiercely debated subject.

Marijuana smoke is actually a combination of more than 400 compounds, although the main psychoactive ingredient appears to be 9-delta-tetrahydrocannabinol (THC). Marijuana is usually smoked, which results in a higher absorption of THC than if taken by mouth. Pharmacokinetic studies reveal that THC is fat soluble and accumulates in body tissues, often lingering for a month after a single dose.[19]

Acute intoxication produces an anxiolytic effect, although the effect is strongly dependent on subjective and environmental cues. Some users report anxiety and panic lasting throughout their intoxication, usually from 2 to 4 hours. There appears to be some evidence of reverse tolerance in experienced users, but heavy marijuana use produces a physical tolerance as measured by subjective ratings of intoxication and objective criteria such as heart rate.[20] There is no abstinence syndrome, but a psychologic dependence is seen in some adolescents.

Controlled studies have shown that smoked marijuana is a bronchodilator in experimentally induced asthma.[21] However, the heavy and chronic use of marijuana, like cigarette smoking, can cause or exacerbate pulmonary disease. Long-term studies have not been completed so the effects on the lung cannot be adequately measured.[19]

In the past, a great deal of interest surrounded the prescription of marijuana to patients with glaucoma. Although marijuana effectively reduces intraocular pressure, its use for glaucoma still is experimental. It also has been reported to be useful in seizure control[22] and in alleviating the nausea associated with chemotherapy.[19]

Most attention has focused on the medical risks rather than uses of marijuana. Due to its increased use and improved techniques for detecting it in serum, marijuana has been associated with more adolescent automobile accidents and deaths.

A great deal of controversy has centered on the personality and cognitive effects of heavy marijuana use. The precipitous skid of the teenage marijuana "addict" into a realm of unrestrained sex, violence, and criminal insanity as depicted in the 1930s film *Reefer Madness* has been disregarded. However, marijuana does appear to impair short-term memory and learning tasks[23] and could have significant effects on the academic and social progress of the approximately one out of 10 high school–aged students who reportedly smoke it daily.[1] An associated "amotivational syndrome" characterized by a blunting of affective range, with general apathy and lack of serious involvement in people and activities, has been observed in some heavy users.[24] Whether this represents an effect of marijuana in some persons or an associated finding in a particular group of troubled teenagers remains to be seen. Schizophrenics should avoid marijuana.

A number of reports suggest that marijuana affects neuroendocrine function. Hypotestosteronemia, gynecomastia, oligospermia, decreased sperm motility, and an increased number of abnormal sperm have been described in males who are heavy marijuana users.[19] In both males and females, THC decreases levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH).[19] Young women who smoke marijuana at least three times a week have a 32% incidence of abnormal menstrual cycles compared to a 12% incidence in controls. This group also had a decrease in serum prolactin.[19]

Several studies have failed to find an association between marijuana use and chromosome damage or birth defects in humans,[25] although recently there has been some evidence of an increased incidence of low birth weight, shortened gestation, and mal-

formations in the offspring of marijuana users.[26] THC does cross the placenta, and in high doses has been said to cause congenital defects in animals.[27]

Hallucinogens

Lysergic acid diethylamide (LSD), a synthetic compound, and mescaline, peyote, and psilocybin are classified as hallucinogens. Hallucinogens enjoyed their greatest popularity in the late 1960s and early 1970s among youth seeking a pharmacologic mystical experience. The use of these substances has decreased, but appears to be making a comeback in a second generation.

The pharmacology of the hallucinogens is diverse, but these compounds generally affect the central nervous system through interference with normal monoaminergic synaptic transmission. They heighten the senses and often create visual, tactile, and auditory hallucinations and illusions. Although no physiologic dependence develops and hence no abstinence symptoms appear, tolerance to hallucinogens develops quickly.

The primary risks of hallucinogens, particularly LSD, are psychologic. Schizophreniform psychotic episodes have been associated with acute intoxication and at times persist beyond drug elimination. It appears that this occurs primarily in persons with strong evidence of premorbid psychopathology and family histories of psychosis and substance abuse, suggesting that the psychosis is activated rather than induced by LSD.[28]

Other long-term sequelae of heavy LSD use include illusions and hallucinations occurring months or even years after the last ingestion.[29] Persistent personality deterioration is seen in some who have a history of chronic hallucinogen use.

The physical risks of LSD and other hallucinogens include traumatic injuries and death. The impairment of time and space awareness and the deterioration of cognitive and sensory reality testing have been implicated in a number of deaths.

LSD taken during pregnancy had been associated with multiple congenital defects such as limb deformities, but there is no substantial evidence of chromosomal abnormalities or teratogenic effects.[30]

Phencyclidine

There has been an upsurge in the late 1970s and early 1980s in the adolescent use of phencyclidine.[31] Better known as PCP or "angel dust," it originally was evaluated for use as a veterinary anesthetic. It is synthesized easily in covert laboratories and is often sold as LSD or some other substance.

The pharmacology of PCP is complex and unpredictable. PCP generally is taken orally or smoked, and intoxication is marked by nystagmus, elevations of blood pressure and pulse, ataxia, hypersalivation, diaphoresis, and occasionally respiratory collapse.[32] The clinical picture is dominated by a variable sensorium that often includes tactile, visual, and auditory hallucinations, and a propensity to self-destructive behavior or violence. Because of the anesthetic qualities of PCP, the user often is unaware of any serious injury. PCP has been associated with a paranoid, schizophreniform psychosis that persists days, weeks, or months and may represent the activation of an underlying psychotic predisposition.[33] Treatment with antipsychotic agents generally is successful.

Effects on neuroendocrine development and teratogenic effects remain unknown. Of particular concern is a recent report that found evidence of PCP in 12% of random cord bloods at a large metropolitan hospital.[34]

Cocaine

Cocaine is the dry crystalline alkaloid of the coca plant that is indigenous to the mountain areas of Peru and Bolivia. Its powerful stimulant effects have been known for centuries among the people of the Andes who chew the leaf. Almost a century ago Sigmund Freud extensively investigated the possible medical uses of cocaine, and personally experimented with the drug, a practice suggested to have played a part in his more famous psychologic discoveries.

Recently the use of cocaine, particularly among affluent young adults, has gained a great deal of media attention. Cocaine is an expensive drug, garnering a price of $100 to $200 per gram. Nevertheless, in some areas an

estimated 10 to 15% of high school students are regular users.

Cocaine usually is self-administered intranasally, although it also is used intravenously and can be smoked in a form called "free-base," a more potent derivative of cocaine. Topically, it acts as an anesthetic, but it also is a powerful central nervous system stimulant, producing a sense of euphoria, increased energy, and a heightened sense of ability. The effect of cocaine is mediated by stimulating the release of norepinephrine and epinephrine into the synaptic cleft and blockage of reuptake of these neurotransmitters presynaptically. Clinical evidence suggests a physical tolerance and dependence, but this remains questionable. A very strong psychologic dependence on the euphoric and energizing effects of cocaine certainly is found.

Acutely, the effects are similar to any sympathomimetic in that tachycardia, dilated pupils, and mildly increased blood pressure are observed. The lethal dose of cocaine is thought to be 500 mg, although most cocaine sold is only 15 to 25% pure.[35] The acute medical risks of low-dose cocaine use appear minimal, which accounts for much of its acceptance among groups generally not involved in the use of hard drugs. However, a number of severe medical, psychologic, and social sequelae occur in the chronic user. Chronic nasal sinus problems and perforation of the nasal septum have been observed. A number of deaths have been reported following oral or nasal ingestion that led to generalized seizures and cardiopulmonary collapse.[35] Cocaine with concomitant use of monoamine oxidase inhibitors, tricyclic antidepressants, alpha-methyldopa, and reserpine can lead to an adrenergic crisis.[36] Hyperthermia presents another life-threatening cocaine reaction as a result of increased peripheral heat production and possibly a direct effect on the hypothalamus.[36]

Free-basing describes the conversion of cocaine hydrochloride to cocaine sulfate. Free-base is smoked and toxic adrenergic reactions frequently occur. The chemicals used in the conversion process are highly flammable and have been implicated in serious burns.

The progression to around-the-clock use is accompanied by serious physical malaise and depression between doses, and the intoxication can be associated with increasing tremulousness, cognitive disorganization, paranoia, and hallucinations that usually are visual ("snow lights") and tactile ("cocaine bugs").[37]

The social consequences are related to the shift in lifestyle, the gradual impairment in functioning, and the energy required to financially support a heavy habit. Some persons reportedly spend more than $100,000 a year on cocaine.

Treating cocaine abuse is very difficult. Cocaine abusers, despite minimal or no physical abstinence, find the euphorant effects of the drug the only relief from profound depression during early abstinence.

Amphetamines

Amphetamines have been abused as stimulants since the 1930s, an era in which they were used in many over-the-counter preparations. Phenylethylamines, amphetamine sulfate (Benzedrine), d-amphetamine (Dexedrine), and methylamphetamine (Methedrine) all have similar stimulant or excitatory effects on the central nervous system, the peripheral nervous system, and the cardiovascular system. The amphetamines are metabolized in the liver by oxidative deamination, and also are excreted by the kidneys, especially in acidic urine.[38]

Amphetamines are abused because of their ability to produce a sense of well being, euphoria, increased libido, mastery of tasks, appetite suppression, and a sense of increased energy. Amphetamines also are abused by athletes to boost their performance in speed events. Usually, amphetamines are taken orally, although occasionally they are inhaled or used parenterally. In addition to the desired effects of intoxication, the user will have some degree of tachycardia, perspiration, tremor, and confusion.[39] These toxicities may progress to cardiac arrhythmias or systolic hypertension with cerebrovascular accidents or seizures. Episodes of hyperpyrexia are possible following parenteral abuse, and incidents of necrotizing angiitis have occurred.[40]

Tolerance to amphetamines develops rapidly. Physiologic dependence also may develop with amphetamine abuse. There are no easily measured parameters to identify an abstinence syndrome, but fatigue, depression, and a rapid increase in appetite regularly are seen in chronic users who stop taking amphetamines.[38]

The chronic effects of amphetamines include ketosis and chronic malnutrition. In the early adolescent, this nutritional insult can result in growth retardation and menstrual dysfunction. There have not been valid reports of amphetamine use having adverse effects on offspring, but certainly if a chronic nutritional insult occurs during gestation, fetal development may be compromised. The chronic use of amphetamines also may produce or uncover a psychosis. The prototypical "speed freak" can present symptoms indistinguishable from an acute paranoid schizophrenic.

Opiates

Opiate use and addiction in adolescents fortunately is infrequent. However, the 10% of high school seniors who reported they had "ever tried" opiates and the 1% who admitted to having used heroin probably do not represent the total adolescent population because opiate addicts frequently are high school dropouts.[1] While opiate addiction is most common in urban lower socioeconomic groups, it is found in adolescents from all walks of life.

The most commonly used opiates are heroin and morphine. Recently the use of pentazocine (Talwin) in combination with the antihistamine tripelennamine (PBZ), or Ts and Bs has replaced heroin in some areas. Opiates are addictive narcotic agents that produce analgesia through interaction with specific endorphin receptors in the central nervous system. An intense euphoria upon the drug's intravenous administration is followed by sedation and progressive CNS depression. Overdoses frequently occur because of the unpredictable potency of street opiates and are characterized by unresponsiveness or coma, respiratory depression, and miotic pupils.

The treatment of opiate-induced coma with the specific opiate antagonist naloxone (Narcan) is effective, and has led to naloxone being administered as part of routine emergency room protocol in the management of the comatose patient. However, naloxone can precipitate abstinence symptoms in the addict, who is found comatose secondary to a mixed overdose or trauma.

The regular use of either oral or parenteral opiates leads to the development of tolerance and physiologic and psychologic dependence. Twenty-four to 48 hours following a heroin dose or 36 to 72 hours after a methadone dose an addict will have an intensely uncomfortable symptom complex of chills, restlessness, muscle cramps, diarrhea, rhinorrhea, anorexia, and vomiting. The untreated abstinence syndrome generally is not fatal and is only rarely associated with seizures.

Gradual detoxification from opiate addiction has been accomplished by methadone replacement in patients 16 and older. In younger patients the use of diazepam (Valium) has been found to shorten the abstinence syndrome from the typical 10 to 14 days to 3 to 4 days.[41] Clonidine, a specific alpha$_2$-receptor agonist that produces a decrease in noradrenergic activity in the central nervous system, recently has been used successfully in opiate detoxification.[42]

Medical complications involving multiple organ systems are associated with both direct opiate effects and parenteral administration.

Intravenous use of relatively impure substances leads to superficial thrombophlebitis, scarring, and "tracks." The scars can be disfiguring and have negative social consequences; sometimes they require surgical removal.

Subcutaneous injection or "skin-popping" is associated with fatty necrosis and the formation of abscesses. Injection of foreign bodies such as mannite, which is used to cut heroin, can cause embolization and cause tissue necrosis. Pentazocine injection may produce a characteristic woody sclerosis of the skin.[43]

Infectious complications frequently are seen in the parenteral drug user. Skin and soft tissue infections are most common, although there is also an increased risk of tetanus. Moreover, adolescents who are parenteral abusers have an increased frequency of hepatitis A and B. Parenteral drug users also are at higher risk of developing acquired immune

deficiency syndrome (AIDS), although opiates have not directly been associated with immunologic defects.

Thrombophlebitis and acute bacterial endocarditis involving the right side of the heart are seen with parenteral contamination. The endocarditis involves a previously normal tricuspid valve and usually is caused by *Staphylococcus aureus* with a significant number of mixed staphylococcal-candidal infections. Frequently fever is the only symptom.

Left-sided endocarditis also is more common in parenteral abusers and usually is accompanied by evidence of systemic infection. There is an increased frequency of involvement of abnormal valves, although normal valve involvement also increases. The most commonly seen infectious agents are staphylococcus, gram-negative organisms, and *Candida*.

Systemic embolization into the arterial system can lead to central nervous system involvement including stroke. Abscesses, particularly multiple microabscesses that produce few neurologic signs, can present as fever of unknown origin. This population also has an increase in hematogenously seeded osteomyelitis.

Gastrointestinal effects commonly are seen. The most common side effect of either heroin or methadone addiction is chronic constipation that can lead to hemorrhoids, which are otherwise rare in adolescents.[44] The risk of viral hepatitis has been mentioned, and is related to contamination of needles and other drug paraphernalia. It is not uncommon to find foreign body granulomata in the liver. The increased incidence of peptic ulcer disease seen in adult addicts does not appear to exist in addicted adolescents.

The pulmonary complications of heroin addiction in adolescents usually are related to aspiration, foreign body reaction, or pulmonary emboli. Pulmonary edema often is seen with acute overdose. Complete resolution can be expected with intubation and oxygen delivery with positive end-expiratory pressure.

A small number of adolescent opiate addicts have proteinuria and/or glycosuria.[45] Focal membranous glomerulonephritis associated with swollen glomerular tufts and endothelial thickening due to deposits of complement and immunoglobulin complexes is seen occasionally and related to immunologic reaction to either the heroin or an injected impurity. Renal failure secondary to massive myoglobinemia associated with the crush syndrome in the overdosed patient or from rhabdomyolysis with deep "skin-popping" (subcutaneous or intramuscular injection) has been described.[46] Amyloidosis of the kidney also has been reported.[47]

In addition to the infectious complications involving the central nervous system, peripheral neuropathies, acute transverse myelitis, and increased intracranial pressure have been documented in the opiate-addicted population.[44]

The use of opiates by the female is associated with secondary amenorrhea and a decreased pregnancy rate. There is evidence of decreased gonadotropin secretion in both males and females, resulting in lowered testosterone levels in the male.[48]

Prostitution frequently is a source of income for the opiate addict; therefore the complications of venereal diseases, especially salpingitis, are common, as is trauma.

The association between opiate addiction in the mother and small-for-date neonates is well recognized.[49] Opiate abstinence symptoms can be seen during the neonatal period in the infants of addicted mothers.[50] There also is evidence of developmental difficulties among the offspring of addicted women, combined with social sequelae of opiate addiction such as family fragmentation, child abuse, and violent and criminal activity. The children of addicted mothers represent a population at risk for future medical and psychologic problems.[44]

Inhalants

Volatile substances, chemicals that rapidly transform to a gaseous state at normal air pressure and room temperature, have been attractive substances of abuse. A variety of drugs are included in this category.

The vasodilator amyl nitrite has been a popular inhalant in its medicinal form (poppers) or in butyl nitrite, an over-the-counter drug sold under the guise of a room deodorizer.[51] It appears that these agents are

most frequently, although not exclusively, used by male homosexuals because of a purported enhancement of orgasm. This perception may be based on a sense that time is slowed, which accompanies the relaxation of smooth muscle in arterial walls, including those of the meningeal arteries, and systemic hypotension that produces cerebral hypoperfusion. In addition, an increase in sexual aggressiveness or a decrease in inhibition has been described. From experience in studying humans exposed to nitrite inhalation both in industry and in the treatment of angina, it is clear that tolerance develops and larger doses are required.[52] No physiologic withdrawal syndrome has been identified.

Health concerns in the inhalant user include frequent headaches, nausea, and dizziness. Syncopal episodes associated with abrupt hypotensive episodes are not unusual. Electrocardiogram changes (transient ST depression and inversion of T waves) are seen.[53] There is a risk of inducing methemoglobinemia. There are no documented or theorized effects either on reproductive potential or of teratogenesis in the offspring.

Toluene and toluene-containing products have had documented abuse for more than 20 years. It appears that it is inhaled most frequently by Hispanics, native Americans, and poor whites.[54]

Toluene, or methylbenzene, is a volatile hydrocarbon that as a solvent has a great affinity for lipids.[55] In high doses it appears to cause a rapid dissociative effect. It may lead to a loss of consciousness and death from suffocation (many inhalers breathe fumes from plastic bags) or exposure. While acutely intoxicated, inhalers may become violent, and traumatic injuries may occur. Tolerance does not appear to develop. However, regular users have abdominal pain about 24 hours after the last dose.

The chronic use of toluene affects several systems. There is documentation of cerebral cortical atrophy,[56] acute psychosis, cerebellar dysfunction, and peripheral neuropathy.[57,58] Both renal tubular and glomerular disease have been described.[59] One study has described a group of toluene abusers who developed pulmonary function consistent with a panlobular emphysema, which was found in the lungs of two chronic abusers upon autopsies.[60] There does not appear to be any disturbance with either male or female reproduction, but Finnish women exposed to organic solvents more frequently gave birth to infants with central nervous system defects than did their matched-pair controls.[61]

The propellants used in many spray cans may inflict further damage in those who abuse inhalants. When the propellants are fluorocarbons, the sensitization or potentiation of the myocardium to epinephrine puts the sniffer at risk for fatal cardiac arrhythmia and the "sudden sniffing death syndrome."[54]

Gasoline, another volatile hydrocarbon, also is an abused substance. In addition to toluene, it has varying amounts of other chemicals such as benzene, xylene, napthalene, n-hexone, and frequently lead. The acute and chronic toxicity from gasoline includes all risks associated with toluene plus the hepatotoxicity of benzene, the renal toxicity of xylene, and the hematologic effects of napthalene (aplastic anemia) and lead (blocking of hemoglobin synthesis). Lead itself has well-documented nervous system and renal toxicity in addition to its hematologic toxicity.

Treatment

Substance abuse is a complex biopsychosocial problem, and treatment must address multiple issues. The adolescent with a substance abuse disorder often has legal, educational, vocational, and economic needs that must be resolved along with the medical and psychiatric problems.

Treatment is often long-term, and relapses frequently occur. There is no standardized treatment that has been proven superior, although any treatment usually is better than no treatment. An adolescent may respond well to a particular treatment program and poorly to another.

Typically, parents, school authorities, or law enforcement agencies direct the teenager into treatment, and often the problem is advanced by the time intervention begins. Adolescents frequently deny or minimize drug abuse and are often poorly motivated for therapy. Ego deficits such as difficulty in forming interpersonal relationships and poor frustration tolerance further complicate therapy. When

drug abuse represents a response to boredom, alienation, or subcultural reinforcement, viable alternatives must be provided. A significant percentage of polysubstance abusers demonstrate neuropsychologic impairment that persists at least temporarily following the discontinuation of drugs.[62] This organic brain syndrome interferes with learning and problem solving. Concurrent psychopathology such as depression, schizophrenia, and personality disorders must be recognized and appropriate treatment provided.

Effective substance abuse programs often use a combination approach, which includes individual, family, and peer-oriented psychotherapies. Intervention tries to help the adolescent improve conflict management skills, tolerance to unpleasant emotions, and general coping skills without resorting to mind-altering substances.

Outpatient programs such as Alcoholics Anonymous often are successful as primary or adjunctive treatment. These groups work on the principle of self-help with peer group support. Special services such as methadone maintenance and inhalant abuse programs are available in many areas.

Hospitalization is used for two purposes. The first is short-term treatment for medical complications or detoxification. Intermediate-length hospitalization in a residential multidisciplinary treatment center provides the most comprehensive treatment.[63] However, it is costly and some question whether it is any more effective than outpatient treatment.[64] Nevertheless, controlled abstinence and intensive psychotherapeutic intervention may be the only way to halt the progression of substance abuse in some adolescents.

Pharmacologic agents often are essential in the treatment of substance abuse disorders. Gradual withdrawal from alcohol, sedative-hypnotics, and opiates has been discussed. In older adolescents, other pharmacotherapies can be used. Maintenance on methadone blocks the effects of heroin and decreases the incentive to use the illicit drug. Disulfiram (Antabuse) interferes with alcohol metabolism and discourages drinking by producing nausea, vomiting, flushing, and other unpleasant and potentially dangerous symptoms when alcohol is consumed. The effects of disulfiram last 2 weeks and offer protection against impulsive drinking. Psychotropic agents such as heterocyclic antidepressants and lithium carbonate are indicated when clinical psychopathology is present.

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Obstetric Problems 21

J. Patrick Lavery

The sexual revolution of the 1960s dramatically broadened the spectrum of obstetric problems currently seen by physicians and others involved in health care delivery. Of particular concern are the problems of medical and social consequence among teenage populations which are increasing both in frequency of occurrence as well as magnitude.

Premarital sexual activity is on the ascendency among urban adolescents. Thirty percent of unmarried adolescents queried in a 1971 survey admitted to at least one sexual experience and this number has risen to 50% by 1979.[1] Many of these sexual encounters take place without any effort on the participants' part at contraception. Sometimes this is due to ignorance or unavailability of contraceptive agents. However, on occasion, there also exists a lack of desire for protection. Resulting pregnancies create fundamental medical, social, and psychologic crises which can lead to incisive life consequences for the individual. The trend toward sexual promiscuity has cut across all social and racial barriers. In a survey of an urban unmarried adolescent population at the Johns Hopkins Hospital, the greatest increase in intercourse was among whites: a 46% increase from 1971 to 1976, as compared to a 19% increase among blacks.[2] However, with the availability of pregnancy termination in recent years, the proportion of live births per adolescent pregnancy has declined from 67% in 1971 to 49% in 1979.[1] This increasing use of abortion as an alternative to contraceptive measures raises serious moral and social issues which the community at large will eventually have to address. On a more positive note is the finding that complications of pregnancy termination procedures among adolescents have been relatively low.[3]

Recent information suggests that teenagers have lower birth rates than their older counterparts.[2] At the same time, the number of out-of-wedlock births in the United States has significantly increased and is continuing to climb. For example, women under 20 had 100,000 illegitimate births in 1960 and 250,000 in 1978.[2] Ninety-three percent kept their children.

The most recent statistics show that in 1980 there were more than 3,600,000 live births in the United States. Girls under 15 gave birth to 10,169 babies, while 552,151 were born to those between 15 and 19.[4] Although it appears that we have already felt the maximum impact of the 1940s and 1950s "baby boom," the numbers faced today by health care providers still are staggering.

Some have contended that this "baby boom" was a product of a sexual revolution. However, Simon and colleagues describe this cultural event as a "parliamentary reform." They suggest that coital experiences in which adolescents are now engaging are more emotionally intense than the casual and experimental attitude which was heretofore suggested.[5] However, whether the pregnancies occur as a result of "revolution" or "reform," the problems and consequences are significant and require thorough understanding.

Curiously, in contrast, in a study evaluating

Table 21-1. Obstetric Risks Classically Associated with Pregnancy in the Adolescent.

Maternal mortality[a]
Pregnancy-induced hypertension (toxemia)
Anemia
Prematurity
Cephalopelvic disproportion[a]
Low-birth-weight infants
Perinatal mortality
Cesarean section
Substance abuse

[a]Especially in those 15 years of age or younger.

125 adolescents interviewed prior to abortion, Gespert and Falk found the distribution to be almost equal between those with casual relationships (41%) and those with a steady boyfriend (54%).[6] The most significant factor in pregnancy occurrence, however, remained the absence of contraceptive usage in this relationship, whether serious or casual.

Many factors affect the obstetric outcome of the adolescent pregnancy, not the least of which is the intensity of interest of the investigators pursuing the project at hand. Many statistics have been published to demonstrate the high-risk nature of the adolescent pregnancy; indeed, pregnant girls under 15 have a 60% higher maternal mortality rate than older mothers.[7] Other obstetric complications traditionally have been associated with adolescent pregnancy (Table 21-1).

The discussion that follows will review the medical aspects of teenage parenthood. The intrinsic medical problems associated with adolescent pregnancy require special attention but are not insurmountable. It is the author's contention that many problems believed in the past to be inherent to the adolescent pregnancy can be reduced or eliminated with appropriate prenatal care and intervention on medical, social, educational, and personal levels. This intervention should have a positive impact not only on the mother's health, but on the offspring who will be suffering anyway from the intrinsic handicap of having been born to an adolescent. Children having children create problems that need long-term intervention. This is discussed elsewhere in this text.

Why Pregnancy?

The female adolescent is in the midst of a dynamic process to develop her self-image. This maturation process, which occurs over several years, leads her to a life separate from parents and home. Unfortunately, the process is not always orderly. Indeed, because of the many myths about menstruation and fertility, many girls are biologically capable of reproducing long before they think they can.[8] Often conflicts in self-image form the basis of a search for independence and freedom. This time of life exposes the adolescent to new conflicts. The adolescent receives most of her information regarding sex from peer groups and often is poorly informed about contraceptives. For example, one study from a hospital in New York City found that more than 50% of the adolescents interviewed did not use any contraception during their sexual contacts.[9] In another urban study, 68% of those who conceived did not use a contraceptive.[6] A combination of ignorance, peer pressure, and psychologic conflicts sets the stage for potential pregnancies. Adolescents are at a developmental stage in which they tend to deny the consequences of their actions. For the female partner such denial ultimately may result in pregnancy, which only intensifies her stress.

Physical Development

As secondary sexual characteristics develop and menstruation occurs, the female soon

becomes capable of reproduction (Chaper 1). Because ovulation is often irregular, many girls have misconceptions about their ability to become pregnant. Ignorance about both the reproductive organs and contraception contributes to the high incidence of unwanted pregnancy. The large percentage of sexually active adolescents (26–68%)[6,10] who do not regularly use contraceptives compounds this problem.

As puberty begins, physical growth becomes apparent. The growth spurt begins at about 10, peaks at 14, and in 98% of all women is fully complete by 18. Pregnancy at this time adversely can affect a girl's growth.[7]

The growth rate of the pelvis is slower than the development of height. Moerman's work suggests that the growth of the pelvic canal continues beyond the rate of statural growth.[11] She found that the pelvis is smaller and less mature in girls who have early menarche than in their later menstruating peers. This further suggests that young adolescents may have problems in the successful vaginal delivery of an average size infant. This growth discrepancy appears critical in women of low gynecologic age (postmenarchal age).

In a study that reviewed the obstetric complications of adolescents, an increased incidence of cesarean sections was observed in those with a gynecologic age of 1 to 2 years.[12] The authors believed the greater frequency of cesarean sections was attributable to smaller pelvic diamters, a condition that no longer exists after a gynecologic age of 2 years. These data are consistent with Ballard and Gold's observation years ago that ages 14 to 15 divide the line between pelvic adequacy and disproportion.[13]

The stress that lactation may place on the growing adolescent is but one of the critical nutritional problems discussed in Chapter 15. Chan et al[14] noted that the bone mineral content of 12 lactating adolescents was significantly below that of a comparable number of lactating adults. This suggests greater nutritional needs for lactating adolescents, particularly during continued growth.

Associated Medical Problems

The lifestyle of the adolescent may be an underlying cause for obstetric problems. Studies have shown that low socioeconomic status, poor nutrition, substance abuse, smoking, venereal disease, and other factors can interfere with an adolescent's chance of a successful pregnancy.

Antenatal care is perhaps the most influential factor in determining a favorable outcome for an adolescent pregnancy.[15,16]

The incidence of several critical medical problems is reviewed in Tables 21-2–21-4. The format of these tables divides the studies between those with retrospective population data where adolescents have been selected out of larger population pools and those studies with adolescent management programs. In many cases the data show how collaborative efforts have improved outcome.

The papers on adolescent pregnancy cited cover a large time span. Furthermore, the selective definition of each reviewer's population and varying socioeconomic population groups will influence statistics. The age of the study population and the year of publication are included to assist the reader in putting the results in perspective. Further details must come from the original publications.

The 1970s and early 1980s have been years of dynamic change in the practice of obstetrics. Higher cesarean section rates, neonatal intensive care units, patient transport, and team approaches to health care have all contributed to improved care and have been successful in influencing statistics on the outcome of adolescent pregnancies.

Pregnancy-Induced Hypertension

Pregnancy-induced hypertension (PIH) or toxemia is unique to pregnancy and is manifested by hypertension, proteinuria, and edema. Whereas approximately 5% of the general population develops PIH, the condition is traditionally associated with the young adolescent.[17] Some believe this is the most prevalent medical complication of adolescent pregnancy.[7]

Factors such as low socioeconomic status, poor nutrition, and poor prenatal care have been associated with toxemia. But until the etiology is better understood these represent associations, and are not causal. It appears, however, that intense antenatal programs do reduce the incidence of PIH. Table 21-2

Table 21-2. Pregnancy-Induced Hypertension (Toxemia) and Adolescent Pregnancy.

Series	Year	Cases	Inclusive Age	Incidence (%)
	Adolescents in the Population			
Coates[18]	1970	137	≤ 14	15
Duenhoelter[19]	1975	471	≤ 15	35
Clark[20]	1982	2280	≤ 16	15
O'Brian[21]	1982	314	≤ 16	17
Ryan[22]	1975	222	≤ 19	18
Osbourne[23]	1981	715	≤ 20	7
McKilligin[24]	1978	371	≤ 20	17
	Adolescent Projects			
Briggs[25]	1962	201	≤ 16	3
Youngs[26]	1977	202	≤ 18	3
Pillari[27]	1980	127	≤ 18	5
Graham[28]	1981	744	≤ 18	9
Lavery[29]	1975	1133	≤ 19	4

summarizes several studies where the problem was reviewed. There appears to be a lesser frequency of pregnancy-induced hypertension in programs specifically designed for the adolescent than in other retrospective studies of the general population.

This suggests that care can indeed influence the outcome, and that toxemia is not necessarily associated with the adolescent. However, favorable results require intense prenatal intervention and effort on the part of health care providers. Other authors are not so optimistic and believe that this population has an intrinsic predisposition to PIH not amenable to change.[30]

Anemia

Anemia, usually the iron deficient type, is a critical problem that often results from adolescent diets[7] (Chapters 16 and 19). Fad diets, concern about appearance, and lack of education about obstetric nutritional needs are all factors that contribute to inadequate iron consumption. However, those adolescents involved in intense prenatal programs seem to have a lower incidence of anemia (Table 21-3). This is consistent with the work of Osofsky et al[32] who found that 95% of a population of pregnant teenagers had diets deficient in iron, protein, calcium, and vitamin A. They con-

Table 21-3. Anemia and Adolescent Pregnancy.[a]

Series	Year	Cases	Inclusive Age	Incidence (%)
	Adolescents in the Population			
Coates[18]	1970	137	≤ 14	19.7
Duenhoelter[19]	1975	471	≤ 15	5.6
Hutchins[31]	1979	1500	≤ 17	11.0
Osbourne[23]	1981	715	≤ 20	11.1
	Adolescent Projects			
Youngs[26]	1977	202	≤ 18	8.0
Pillari[27]	1980	127	≤ 18	5.0

[a]Anemia defined by hemoglobin levels ≤ 10 g-%.

cluded that the incidence of anemia was based on the demographic characteristics of the pregnant adolescent, not on pregnancy per se. Hence, there is a significant need for educational intervention when an adolescent's lifestyle is detrimental to a good obstetric outcome.

Prematurity

Prematurity is the most significant obstetric problem faced today. Preterm birth affects 10–15% of the population and accounts for 75% of the perinatal mortality in the United States.[33]

The definition of prematurity, however, must be clarified. Preterm birth refers to deliveries at less than 37 weeks of gestational age. Many studies refer to low-birth-weight infants (< 2500 g) as premature. Preterm and low birth weight are not necessarily the same and certainly not interchangeable. For example, intrauterine growth retardation may occur in a pregnancy that has extended beyond 37 weeks. In this condition the fetus is deprived of its full growth potential, yet the pregnancy may extend beyond 37 weeks. The problem—not always adequately addressed—is that circumstances associated with intrauterine growth retardation are often found in the adolescent gravida. These include hypertensive disorders, poor nutrition, inadequate care, and congenital anomalies.

Several historical and clinical factors that have been associated with premature birth occur in the adolescent population and form the predisposing basis for preterm delivery. These have been reviewed by Carey et al[7] and include low prepregnancy weight, minority ethnic origin, adverse social conditions, unmarried status, smoking, narcotic use, anemia, primiparity, and deficient prenatal care.

Despite these often-found handicaps, efforts again appear somewhat successful at modifying the overall incidence of this problem, as noted in Table 21-4. These results would suggest that premature birth is not a necessary affliction of adolescent pregnancy, but one that can at least be modified by intense antenatal care.

Cesarean Birth

The adolescent pregnancy has been called "the circumstance of a child having a child." It is frequently emphasized that the growing gravida is expected to have problems related to her still immature state of growth. Many primary cesarean sections are done for cephalopelvic disproportion. At times this phrase becomes a catchall for anything from elective delivery with the presenting fetal part not well

Table 21-4. Prematurity and Adolescent Pregnancy.[a]

Series	Year	Cases	Inclusive Age	Incidence (%)
	Adolescents in the Population			
Coates[18]	1970	137	≤ 14	19.0
Duenhoelter[19]	1975	471	≤ 15	19.2
Klein[34]	1974	5835	≤ 16	17.7
Clark[20]	1982	2280	≤ 16	17.0
O'Brian[21]	1982	314	≤ 16	9.6
Hutchins[31]	1979	1500	≤ 17	16.0
Ryan[22]	1975	222	≤ 19	12.0
McKilligan[24]	1978	371	≤ 20	6.0
	Adolescent Programs			
Youngs[26]	1977	202	≤ 18	17.0
Pillari[27]	1980	127	≤ 18	6.2
Graham[28]	1981	745	≤ 18	14.5
Lavery[29]	1975	1133	≤ 19	6.5
Sherline[35]	1978	1113	≤ 19	9.0

[a]In this compilation, prematurity and a low birth weight of 2500 g or less considered inclusive of both.

engaged in the pelvis to dysfunctional labor patterns with poor progress. Hence, the statistics in many studies may have faulty definitions. In actuality, only about one to three out of ten cesarean sections are for true disproportion.[36] Of critical note, however, is the past decade's tremendous increase in cesarean section rates across the country. Many centers frequently have a cesarean section rate of 15–25%.[36,37] Any review of cesarean section rates should note when the study was done. Most authors[20,21,23,25,27,29,31,34] do not find a greater increase in the incidence of adolescent cesarean birth than in the older population, which suggests that pelvic contracture is not a critical problem (Table 21-5). Other studies[12,19,22] did find a greater frequency of abdominal birth in their adolescent populations. The reason for this discrepancy is unclear. Duenhoelter's[19] series was restricted to youths 15 years old or younger. The rate was 10.4%, high for that time. As suggested earlier, pelvic dimensions at some point in maturation may be too constricting. However, a previous series by Coates[18] had a cesarean rate of only 4.4% for gravidas under 15. The problem of pelvic contracture does not appear to occur after age 16.

Congenital Malformations

Congenital malformations of the neural tube (anencephaly, spina bifida, and meningomyelocele) occur more frequently in the offspring of teenage mothers.[38] The incidence of such defects in the general population is about one in 2000 while in offspring of adolescents it may be as frequent as one in 1000. The basis for this higher incidence of neural tube disorders is speculative. It is curious, however, that an association has been shown between the antenatal ingestion of supplemental vitamins and a decrease in the frequency of neural tube defects.[39,40] It is not surprising that adolescents do not take supplements as frequently as the average adult population.

Perinatal Mortality

Perinatal death is defined as a pregnancy loss—either stillbirth or neonatal death—from 28 weeks of gestational age through the first month of life. Such an event is significantly affected by antenatal factors. Several clinical circumstances such as prematurity, hypertensive disorders, anemia, and congenital malformations are associated with perinatal death. Naturally, some of these factors are more influential on one form of perinatal loss than another. Neonatal mortality, for example, is more influenced by premature birth, while stillbirths are more apt to happen when stressful events such as eclampsia occur in utero. Table 21-6 shows the difference between the perinatal mortality rate in planned programs and in the general popu-

Table 21-5. Cesarean Section and Adolescent Pregnancy.

Series	Year	Cases	Inclusive Age	Incidence (%)
	Adolescents in the Population			
Coates[18]	1970	137	≤ 14	4.4
Duenhoelter[19]	1975	471	≤ 15	10.4
Hutchins[31]	1979	1511	≤ 16	5.5
Clark[20]	1982	2280	≤ 16	6.7
O'Brian[21]	1982	314	≤ 16	12.1
Ryan[22]	1975	222	≤ 19	12.0
McKilligan[24]	1978	371	≤ 20	14.0
Osbourne[23]	1981	715	≤ 20	9.2
	Adolescent Programs			
Lavery[29]	1975	47	≤ 15	2.0
Briggs[25]	1962	201	≤ 15	3.5
Pillari[27]	1980	127	≤ 18	8.7
Graham[28]	1981	745	≤ 18	16.6

Table 21-6. Perinatal Mortality in Adolescent Pregnancies.

Series	Year	Cases	Inclusive Age	Incidence (%)
	Adolescents in the Population			
Coates[18]	1970	137	≤ 14	6.6
Duenhoelter[19]	1975	471	≤ 15	3.0
Klein[34]	1974	5835	≤ 16	3.9
Hutchins[31]	1979	1511	≤ 16	4.0
O'Brian[21]	1982	314	≤ 16	2.5
Ryan[22]	1975	222	≤ 19	5.4
Osbourne[23]	1981	715	≤ 20	1.8
	Adolescent Projects			
Briggs[25]	1962	201	≤ 16	1.5
Youngs[26]	1977	202	≤ 18	0.0
Pillari[27]	1980	127	≤ 18	0.8
Graham[28]	1981	745	≤ 18	3.0
Lavery[29]	1975	1133	≤ 19	2.2
Sherline[35]	1978	1113	≤ 19	3.9

lation. This suggests that the intensity of prenatal care is a significant factor.

In an analysis of the determinants of perinatal mortality, Sacker and Neuhoff suggest that biologic immaturity does not appear the prime factor contributing to perinatal death.[41] In data taken from an urban population, however, Hardy et al,[42] noted a greater frequency of perinatal deaths among black adolescents, particularly those under 14. These findings emphasize an association between perinatal mortality and socioeconomic status and prenatal care rather than biologic dysfunction related to age and maturation.

Maternal Mortality

Limited data suggest the adolescent gravida is at greater risk of maternal death.[41] Fortunately, improved medical and anesthetic management in recent decades has significantly reduced maternal mortality from vaginal and particularly cesarean deliveries to less than ten per 100,000 live births.[37,43] Despite this reduction, the risk for the young mother—particularly if she is under 15—still is greater than that for her older counterpart.[44-46]

Recurrent Pregnancy

Although the problem of a pregnancy during adolescence is critical, recurrent pregnancies are even more of a problem. Efforts to educate adolescents about contraceptives and to counsel them are not always successful. Kappelman reported a 27.9% recurrent pregnancy rate in a teenage urban public school program.[47] In a 3- and 4-year follow-up study in Mississippi, Sherline and Davidson[35] reported repeat pregnancy rates of 18% and 23% among adolescents enrolled in their pregnancy care program.

Klein,[34] on the other hand, showed a decrease from 16.6 to 4.8% in the recurrent pregnancy rate of patients under 16. This held true when continued follow-up was maintained in an intraconceptional clinic. Intense efforts at education can indeed decrease the frequency of recurrent adolescent pregnancies if contact can be maintained with the patient through programs designed for conception control. The availability of such programs and adolescent compliance, unfortunately, do not always go hand-in-hand. An example is the disappointing experience at the University of Louisville Teenage Parent Program. Despite a comprehensive program that includes educational, medical, and social services in addition to a dedicated staff, recurrent pregnancies for teens under 18 have increased from 4.1% in 1981 to 8.8% in 1983. Even the incidence of third pregnancies has increased from 0.2% in 1981 to 1.7% in 1983.

It appears that despite educational inter-

vention and contraceptive availability, the problem of adolescent pregnancies requires more intense efforts at understanding the adolescent female's psyche rather than just her physiology.

The Solutions

Reycroft and Kessler noted in an editorial on adolescent pregnancies that, "During the 1970s it became increasingly clear that the teenage pregnancy was primarily a sociologic problem with medical consequences."[48] Thus, the emphasis must be on comprehensive screening for recognized risk factors, intense antenatal care, and thorough follow-up to ensure appropriate contraception after delivery.

Several of such programs have been successful both in improving the outcome of adolescent pregnancies and reducing recurrence rates.[28,29,35,47,49] The St. Paul,Minnesota Project[49] in its first 3 years was able to reduce the pregnancy rate in the high schools involved from 7.9 to 3.5% and avoided recurrent pregnancies totally.

This approach of "integrated family life education," which combines care, education, and accessibility to contraception, appears to help reduce the epidemic of adolescent pregnancies.

The advantage of such integrated educational programs is that they expose adolescents to biologic facts and contraceptive techniques before the pregnancies occur. Freeman and Rickels[50] found that more than 80% of some adolescents have had intercourse before requesting contraceptives. Unfortunately, in many cases increased promiscuity is seen among adolescent groups with significantly less knowledge about contraceptives than in control groups.[51]

Despite efforts to encourage community acceptance, there are handicaps to the expansion of successful adolescent education and contraceptive programs. Sherline and Davidson[35] found that few agencies or physicians were interested in referring patients to their teenage pregnancy program, despite several years of intense public education and advertising. If society is not aware of the problem, it cannot be solved.

The factors that are thought to encourage better patient continuation rates in the St. Paul Project include (1) personalized services with guaranteed confidentiality; (2) free and accessible services; and (3) educational services that include partner involvement prior to the medical encounter.[52]

As noted above, integrated efforts do not guarantee success. Professionals must seek a better understanding of adolescent motivation.

Venereal Disease

The frequency of venereal disease appears to be on the rise, especially among adolescents. The highest risk group of the over 2.5 million women treated for gonorrhea in the United States are among single women age 15–24.[53]

Gonorrhea ranks first among reported communicable diseases in the United States, and the 15–19 age group has an incidence second only to those aged 20–24[7] (Chapter 17). Other venereal diseases such as herpes infection are on the rise and could have significant obstetric consequences.

Resources

Wallace et al[54] recently assessed services for pregnant teenagers in large American cities (population > 100,000). Eighty-three percent (127) of those queried responded. They reported that significant deficiencies appear to be present in light of our understanding of the medical and social nature of the problems of adolescent pregnancies. They found that only 64% had sex education programs, 61% had social services integrated into their programs, only 42% had special contraception programs, 41% had special medical care programs, and only 26% had specialized psychiatric services. Despite intense publicity and public information generated about adolescent pregnancy, these authors[54] found that only five cities had developed new programs since 1976, the last year surveyed before 1980. The problem of adolescent pregnancy will not go away. Moreover, such projects need not be exorbitantly expensive. In the 1970s, a Maryland educational project was funded in two rural areas for only $57,000, and in 3 years it was

able to decrease the fertility rate among 15- to 19-year-olds from 8.4 to 5.6%.[48]

The Children of the Child

The data regarding long-term follow-up and the consequence to the offspring of adolescent parents are limited. As late as 1976, it was noted that "systematic research on the consequences of adolescent parenthood is virtually nonexistent."[55] As several projects have developed, more information has become available. Baldwin and Cain[56] said that "the children of younger mothers showed decrements in terms of cognitive development, were more likely to live in one-parent homes, and also showed more early childbearing themselves as compared to children of older mothers."

The Johns Hopkins Child Development Study also addressed this subject. It found significant developmental differences in the offspring of adolescents, particularly among blacks.[42] It suggested this may be related to the many variables that influence the quality of the offspring's life and development.

This echoed Baldwin and Cain's comment that these effects "do not result from the mother's age at birth directly but rather are transmitted through other factors associated with early childbearing such as educational and economic disadvantage and a greater likelihood of marital breakup."[56] It has been suggested that social adaptation and psychologic well being can be supported by a father or grandmother living in the offspring's home. Thus, Kellam et al[57] suggest that offspring living in homes made up of only the mother have the greatest risk of psychologic maldevelopment.

Childrearing places great stress on both the child and "woman-child," with potentially serious consequences for each.[58] Economic stress, emotional pressure, and role formation are all critical, and solutions are not always apparent or available.

Summary

The young gravida is at risk for obstetric, social, educational, and life problems. Although there appears to be no intrinsic handicap to a successful pregnancy during adolescence, the course to such an end is not easy.

The essential value of prenatal care in improving pregnancy outcome has been demonstrated.[15] However, this does not take into account the preconception and postpartum periods. It is during these times that intense educational and supportive efforts must be given. Thus will the "syndrome of failure" associated with adolescent pregnancy as described by Klein be ulimately avoided.[34] Indeed, it is the health care providers that have failed to create a positive atmosphere of education and guidance for a segment of our society that is in emotional and physical turmoil.

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Pregnancy and Parenting: Psychosocial Perspectives 22

Elizabeth A. McGee and Laura Schiller

Parenthood comes too early to many American young people. A higher proportion of American teens become mothers than do their counterparts in other developed countries with the exception of those in Eastern Europe. Every year more than 1 million American teenagers become pregnant, most by accident. Half of these young women continue their pregnancies to term and 40% of teen mothers are under 18. The majority are not married when they become pregnant, and nearly all keep their babies.[1]

The problems associated with teenage parenthood have been amply documented.[2] Over the past three decades, as adolescent sexuality, pregnancy, and parenthood have attracted increasing national attention, substantial research into the antecedents and consequences of adolescent childbearing has been conducted. Teenage childbearing is clearly linked to economic and social disadvantages for young parents and their children. Most studies have focused on young women and consistently show that early parenthood sets severe limits on young mothers' lives and results in substantial public expenditures. Half of the budget of Aid to Families with Dependent Children (AFDC) goes to households in which the mother bore her first child as a teenager.[3]

Recent interest in this burgeoning problem has led to research, government policies, and services that have enjoyed some success. For example, the school dropout rate among pregnant adolescents and teenage mothers has been reduced, the incidence of births to teens has declined, and the medical risks for young mothers who receive adequate prenatal care are nearly the same as those for adults with similar backgrounds.[4] Nevertheless, the problems of adolescent parenthood require continued attention: the pregnancy rate for teenagers is rising, the birth rate is declining only among married teens, and about half of all pregnant adolescents do not get prenatal care in the first trimester.[5]

While every community offers some services for sexually active, pregnant, and parenting teens, the impact is limited because they are used by only a fraction of those who need them.[6] Too many services are geared to pregnant young women, yet offer little to young fathers and mothers after the birth of their child. Poor location and limited hours often impede their accessibility and usefulness. Moreover, few communities coordinate their services so that teens can make more effective use of them; no one helps teens navigate the complex array of existing services. Nor is there adequate community collaboration to develop additional resources, strengthen existing services, or experiment with strategies to help these teens.

Despite these service delivery problems, some program models have demonstrated a positive impact on the lives of their clients.[7] These programs provide young mothers with comprehensive services through an integrated service delivery system. Usually they provide individualized care for a small number of clients. Unless public funding priorities change, however, such models are too ex-

pensive to duplicate in many communities. Instead, we must focus on changing or supplementing the existing service system by institutionalizing innovative approaches that appear to be effective.

Patterns of Teenage Sexual Activity, Contraceptive Use, Pregnancy, and Childbearing

Surveys of American teenagers' sexual behavior conducted in the 1970s have documented a substantial change in the proportion of teenagers who have sexual intercourse.[8] By 19, half of all unmarried young women have had intercourse. For many young people, having a close, steady relationship with a person of the opposite sex naturally includes intercourse. Other teenagers have sex for status, because of peer pressure, or to satisfy their need for closeness. Sexual activity most commonly occurs in the teenager's home.

Most young couples use contraception erratically if at all. Teenagers have many misconceptions about the risks of pregnancy and the possible side effects of contraceptives. They are reluctant to plan for sex because most feel that premarital sex is wrong. Therefore, to prepare for it by obtaining a dependable method of contraception is to prepare to be "bad." In addition, they are worried about encountering disapproval from the professionals who might help them.

Pregnant teens' most common observation is, "I didn't think it would happen to me." This reflects immature cognitive development and predisposes them to what adults view as irrational behavior.

Teenagers also have difficulty using contraceptives because they are inexperienced at arranging for their own health care. They are also novices at the communication and negotiation required in an intimate relationship, and as a result seldom rely on their partners for help with contraception decisions. Furthermore, they worry about being seen getting medical services for family planning, and they are fearful of gynecologic procedures—especially the use of the speculum. Self-conscious about their bodies, adolescents are reluctant to be examined or to even touch themselves in the course of using a contraceptive. Finally, current contraception methods are not especially suited for the impulsive teenage population.

Thus, the problems of obtaining and using contraceptives are often more immediate and overwhelming than the thought of a possible unwanted pregnancy. For similar reasons, some young women who might otherwise opt for abortion do not.

In 1979, 1.5 million teenagers sought family planning services.* This is only a small proportion of the youngsters who are sexually active. The average young woman does not seek contraceptive services until close to a year after her first sexual experience. By that time many have already conceived.[9]

Four of every 10 young women today become pregnant as teenagers. These girls are everyone's daughters, regardless of economic, social, or racial background.

While the *pregnancy* rate for teenagers is rising, the *birth rate* has declined. There were 1,180,450 teen pregnancies in 1980, with nearly half resulting in live births and almost 40% ending in abortion. (The remainder were spontaneous abortions.) The majority of teen births occurred in women 18 and 19, but 40% were younger.

The typical adolescent pregnancy is premarital and unintended. While marriage is usually regarded as an ideal, many young parents see it as having little practical or moral value. This separation of marriage and motherhood has had a predictable result: fewer teens marry because of pregnancy and the out-of-wedlock pregnancy rate has been steadily rising for decades. Since 1970, for example, the out-of-wedlock birth rates have increased by more than 50% among white teens aged 15 to 17. Nearly two-thirds of all teen pregnancies are conceived before marriage.

More than 90% of young mothers keep their babies. Service providers observe today that very few teens are willing to consider adoption.

Teenage parents most often come from communities struggling with the problems of poverty, unemployment, and racial discrim-

*Unless otherwise indicated, all statistics in this chapter are derived from refs. 1 and 8.

ination. Teenagers from low-income families have the highest rates of childbearing, and a disproportionate number of young mothers come from single-parent homes where the mother also began having children as a teenager. Many school-age mothers are school dropouts and severely deficient in basic literacy skills. In summary, then, teenage mothers are among the most needy members of our communities.

For many poor girls, motherhood is seen as a chance to do something that society values. Frequently, they do not perceive ways other than parenthood through which they can pursue the independence, identity, and sense of self-worth that adolescents so intensely desire. Without adequate education, meaningful career opportunities, and successful role models, many girls from troubled or disadvantaged backgrounds do not have the incentives to delay childbearing that those from middle-class or supportive familes have. Experts postulate that a significant proportion of teenagers would be less likely to become parents if there were other options to which they could aspire.

Within a year of giving birth, nearly one out of every five young mothers becomes pregnant again. A second birth for a teenage mother almost guarantees a halt to schooling and employment. In 1978, one-fifth of all babies born to teenagers were second or higher-order births.

Since birth rates are declining for every age group except young teens, a greater proportion of American children are now from young families. In addition, teenagers account for half of all out-of-wedlock births.

Many leaders are particularly concerned about patterns of pregnancy and childbearing among black teens because nearly a quarter of all black children are born to teen mothers.[10] Furthermore, half of all black children are born out of wedlock, with teens being responsible for a significant number.

Although the relationship between ethnicity, sexual activity, and pregnancy resolution is not clear, differences between black and white teenagers are marked, though somewhat diminishing. Black teens have an earlier menarche and have intercourse at a younger age than their white counterparts. By 19, a higher proportion have had intercourse, pregnancy, abortion, and birth. Young black women are less likely to marry because of pregnancy. Eighty-three percent of births to black teens occur outside marriage, compared to 29% of births to white teens.

Family attitude toward early or out-of-wedlock pregnancy has prompted a great deal of discussion. Service providers indicate that most parents, regardless of ethnic background, are disappointed by an early pregnancy. These parents may be willing to accept and even welcome the birth of an unplanned grandchild, but they would prefer that the pregnancy never had occurred.

Antecedents of Teenage Pregnancy and Parenthood

Social mores in the United States have changed significantly over the past two decades, leaving us with no consensus about what constitutes acceptable sexual behavior. All teenagers are influenced by changes such as the following:

The diminishing effectiveness of traditional authority figures and the increasing power of the media, especially Madison Avenue's glamorized and glossy portrayal of sex.

A decline in the double standard, partly as a result of the sexual equality advocated by the women's movement.

The increasing availability of adult-free areas where teenagers can be alone.

A more prevalent acceptance of sexual activity and childbearing outside of marriage.

As a result of these and other reasons, an increasing proportion of American young women have sex and become pregnant during their teenage years.

Only half of those become pregnant, however, actually become mothers. The psychosocial characteristics of teenage mothers are similar to those of school dropouts, unemployed youth, and delinquents. Teen parents, like other troubled teenagers, often have poor self-esteem, low aspirations, poor academic achievement, low-status families, or difficult parent-child relationships.

To become mature, responsible adults, adolescents must imagine future possibilities that seem attainable, satisfying, and conducive to

personal and economic independence. The next step is preparing themselves to make these possibilities a reality, a process that in our society can take a long time. This entire process is profoundly influenced by the adolescent's family. Moreover, the cultural meanings attached to being male or female have an especially marked effect on identity formation and behavior.

As adolescents separate from their parents, work out their choices for the future, and determine their values about sex, relationships, marriage, parenthood, and employment, they are prone to take risks, experiment, and fantasize. The danger, of course, is that adolescent experiments with sex and intimacy can lead to an accidental pregnancy. Teens are faced with decisions that they are often neither emotionally nor intellectually prepared to make.

Some teenagers who decide to become parents are stable and mature enough to manage this choice. For others, however, early childbearing is a symptom of complex problems. The usual sequence of adolescent development has not proceeded on course for these young people. Premature parenthood is often a response to frustration, whether environmental or emotional. It can be a form of rebellion or an expression of anger, alienation, apathy, or ambivalence, all of which are common emotional states during adolescence.

While parenthood appears to offer a promising future that is easily within their grasp, most young parents are in fact unprepared for this choice. Parenthood often severely complicates life and signals a premature end to adolescence.

Despite radical role changes and broadening career opportunities, young women in many ways still are taught to focus on physical attractiveness, motherhood, and homemaking. They often are discouraged from pursuing careers or taking work outside the home seriously. Young women from poor or troubled homes frequently know few people who have had happy marriages or rewarding jobs.

Childbearing, for these young women, seems as likely—if not more likely—to bring happiness. Lacking the motivation to obtain contraception, they passively allow an accidental pregnancy to occur. They then drift into parenthood with only a hazy sense of what lies ahead. Or they intentionally get pregnant in hope of solidifying a relationship. Often they imagine that the benefits of motherhood will be greater than they really are.

On a psychological level, early childbearing is a way of coping with adolescent conflicts about role, identity, and self-esteem. It also can represent a way of acting out more individual problems. Young mothers can be, for example, looking for love, struggling with Oedipal ties, using the baby to recoup an emotional loss, trying to be successful at something, or seeking relief from the conflict between her need to be both dependent and independent.[11,12]

Young Mothers and Their Families

The relationship with the family is critical to well being during pregnancy and after birth, particularly for those who are unmarried or of school age. These teenagers tend to rely on their mothers and other relatives for emotional support, financial assistance, and help with child care.[13,14]

While for many teenagers becoming a parent signals the beginning of adulthood, it is not so clear for their families. Most teens want the privileges of adulthood, yet many do not understand the demands and responsibilities it brings—a fact their families are quick to recognize. Hence, young parents' families are both the principal source of support and a major source of conflict.

Most unmarried mothers of school age live in their parents' home. This can create a tense situation for the new mother as well as for other members of the household because she is cast in the dual role of both parent and child. Moreover, the living arrangement forces her mother to also assume a dual role as parent and grandparent. Inevitably this tension exacerbates normal adolescent ambivalence about adulthood. In addition, living in an intergenerational household intensifies the difficulties the mother may have in learning to relate to her daughter as a mother.

The new baby frequently becomes the focus of this struggle for control. Role definitions

and expectations have to be settled: the family must decide who is to care for the child, what childrearing practices are to be used, and how much time the mother will spend away from the baby. If these matters cannot be negotiated satisfactorily, friction, if not hostility, is likely to occur.

Many unmarried young mothers remain involved with the fathers of their children after birth. However, these relationships are often stormy, and do not offer an alternative to family support. Furthermore, teen mothers' relationships with their partners tend to dissolve over time. Married young mothers get help from their husbands and their husband's families. However, since teen marriages are likely to break up, this source of support is unreliable. This makes the girl's family the linchpin of her entire support system and often the focus of her frustration and confusion.

Consequences of Teenage Pregnancy and Parenthood

Almost 40% of all pregnant teenagers opt for abortion. They tend to be girls of higher social class, for whom delayed childbearing means access to satisfying options for the future. Very few young women have any long-term difficulties as a result of abortion; those who do usually have preexisting emotional problems more severe than those of normal adolescence. While childbearing disrupts a teenager's life far more than abortion, it nonetheless can be a painful, expensive, and sad way to end a pregnancy.[15]

Teenage parenthood disrupts life by interfering with normal preparation for adulthood. It is likely—though not inevitable—that parenthood will lead to more lasting problems, especially if the teenager is female, a minority, poor, or younger than 18.

The negative consequences of teenage pregnancy frequently are a result of circumstances of the young mother's family. Many teenage mothers have greater difficulty becoming mature and economically self-sufficient because of socioeconomic, family, and psychologic problems. At the same time, the social and economic limitations of early parenthood are enough to create problems and curtail opportunities.

The adverse consequences of teen parenthood are well established.[16,17] Early childbearing, combined with an individual's background and motivation, affects a young mother's educational attainment and poverty status. Many teen mothers are without adequate education and vocational training, and therefore get stuck in low-paying jobs such as clerical, service, or factory work. They are likely to be intermittently unemployed and, as a result, frequently dependent upon public assistance. Furthermore, teenage marriages are particularly unstable so most young mothers spend some time in their lives as a female family head. Finally, the children of teenagers are usually less healthy, less academically successful, and apt to repeat their parents' life patterns.[18,19]

The young woman who decides to have a child risks never growing up properly. Teen mothers find it difficult to meet their own needs while responding to those of another developing person, especially when the baby does not fulfill romantic expectations. Most are not ready for the restrictions of parenthood. Living in a three-generational household, independently, or with a man can be daunting. A new parent may find it difficult to finish school, gain job skills, or hold down a job. The stress of early parenthood can exacerbate the normal inter-generational conflicts of adolescence. Locating and navigating their way through the array of services available is often confusing to young mothers. Moreover, the pervasive effects of poverty make the work of meeting basic living needs all-consuming. And, as if these challenges were not enough, many teen mothers soon find themselves pregnant again.

Despite the problems, having a child still seems worthwhile to many young people. For some, the obligations of parenthood are offset by the pleasures of rearing a child. Many are able to cope with the challenges. Fortunately, teen parents have many strengths to draw upon. Like most adolescents, they are usually energetic, open to learning, flexible, and optimistic. Initially, at least, they tend to be proud of their babies and eager to do right by them. These parents with adequate support

can often stabilize their lives and finish the psychologic and practical work of preparing for adulthood and at the same time provide for their children.

Teen parents who get both economic and psychologic support from their families have less disruption to their lives as a result of early parenthood.[20] However, because a disproportionate number of teen parents come from deprived backgrounds and because an accidental out-of-wedlock pregnancy presents at least a temporary crisis for most families, many need help from community services. Adolescent mothers who are isolated from both formal and informal networks of support are the most vulnerable to problems which will affect their ability to care for themselves and their children.

Innovative Strategies for Helping Sexually Active, Pregnant, and Parenting Teenagers

The continuing increase in adolescent pregnancy is a clear indication that more must be done to help teenagers prevent unintended pregnancies. Intervention to reduce the incidence of teenage pregnancy will have to include measures to better educate teenagers on the use of contraceptives, to motivate them to continue access to family planning services, including abortion, and to protect teenagers' right to confidentiality, and use of birth control. Efforts to reduce teenage childbearing also will have to involve broader strategies for reducing poverty and helping disadvantaged families.

New approaches to pregnancy prevention are likely to include the sharing of resources through community coalitions and interagency collaboration. Other innovations include professional consciousness raising, programs to help parents to better discuss sexuality with their children, use of the electronic media, outreach networks, and new functions for regular and alternative schools. Experiments with all of these approaches are currently underway:

1. In 1978, Columbia University's Center for Population and Family Health at the School of Public Health began to develop new programs to more effectively serve the Washington Heights community. Washington Heights, the upper Manhattan neighborhood where the Columbia-Presbyterian Medical Center is located, is primarily Hispanic, many of whom are illegal aliens. The teenage pregnancy rate is high. The center wanted to make the community more aware of the risks of adolescent childbearing, educate teens about pregnancy prevention, and improve teen family planning services at Presbyterian Hospital. Through a series of imaginatively designed outreach projects and a carefully restructured young adult clinic, the center is trying to create a partnership in which the medical center can be more responsive to community needs and the community can use the center's services more effectively.
2. The Santa Barbara, California, Girls Club has developed a course for 9th grade girls built around an inviting workbook called *Choices: A Teen Woman's Journal for Self Awareness and Personal Planning*. The Center for Population Options in Washington, D.C., is developing a life-planning curriculum for teenagers that links sexual and vocational decision making.
3. In Tacoma, Washington, a 30-segment soap opera called *General High School* has been produced by the county health department using local high school students for the script, music, and acting. The negative consequences of early childbearing are dramatized. Local radio stations donate air time for the 60-second spots and then provide information on community services.
4. Staff of member health, welfare, and social service agencies at the Brooklyn Teen Pregnancy Network at the Brooklyn YWCA in New York City gather every 6 weeks to share information and inservice training. In addition, the network provides outreach and referral services, and acts as an advocate for sexually active, pregnant, and parenting teens.

Although services and special programs available to pregnant and parenting teens are diverse in most communities, they are not

always effective.[20] A number of model projects, however, have been successful in reducing the number of medical complications during pregnancy, improving infant health, encouraging school enrollment or completion, and reducing the repeat pregnancy rate. Most studies have found it is easiest to improve the medical outcome and hardest to reduce the incidence of repeat pregnancy.

The best programs follow institutional arrangements and procedures found effective in helping high-risk youth or poor and minority women. Comprehensive services are offered through an integrated delivery system which uses a number of agencies. Most programs are available at one site so teenagers will not have to navigate through more than one facility. Care is geared toward the individual's particular needs and is available over an extended period. Strong leadership and a competent multidisciplinary staff create structure with flexibility and warmth.

Most of these programs focus on young mothers because they are easier to identify and recruit and have an immediate need for services. While providers are concerned about young fathers, ambivalence toward them and the limited availability of resources have led most to devote their energies to the teenage mother. Nonetheless, many programs encourage fathers to participate in an attempt to strengthen the young man's identity with fatherhood. However, actually we know little about how to help these young men. Many experts assume that young fathers need jobs more than anything else.

Comprehensive programs for pregnant and parenting teens generally try to ensure an uncomplicated delivery and healthy infant; keep participants in school until they get their high school diploma or its equivalent; expand knowledge of parenting, child development, family planning, and occupational options; provide assistance with child care; increase young parents' self-esteem and confidence; encourage the involvement of the extended family; and delay future pregnancies. A less tangible but equally important goal is that these programs attempt to nurture the hope that with proper preparation teen mothers eventually can become personally and economically independent.

Service providers are increasingly recognizing the critical role of employment assistance in helping young mothers. Vocational programs improve teenage mothers' future options by providing them needed information, skills, and incentives to finish school and delay additional children. Without support and solid job preparation, many young mothers will be poor and intermittently dependent upon public assistance for the rest of their lives. Without a rewarding alternative to motherhood, many will have a second child while still in the teens. Support for these mothers is crucial if they are to manage both the demands of parenthood and school or work.[21]

A number of new service delivery models now exist for pregnant and parenting teens. These three are being evaluated:

1. Project Redirection is a national demonstration project operated at four sites by the Manpower Demonstration Research Corporation in New York City. The project seeks to redirect the lives of participants by offering comprehensive services for pregnant teens and young mothers who are under 18, have not graduated from high school, are on public assistance, or are living in a welfare-dependent family. Innovative features include assigning each girl to a community woman who acts as a mentor and role model, service contracts, and a strong emphasis on preparing them for the job market.
2. The Teenage Pregnancy and Parenting Project (TAPP), an interagency program at San Francisco General Hospital, offers comprehensive services to clients for up to 3 years. A system of multiple tracks allows TAPP clients flexibility in their use of services. Every teenager in the program is assigned to a "continuous counselor" who personalizes the relationship between the client and the service network while providing continuing guidance, a consistent role model, and support for the young mother and her child.
3. The Urban Affairs Corporation in Houston, Texas, links resources in the private and public sector. It operates an adolescent primary health care center and

child care facility at an alternative high school in a low-income community. Recently they have added a training and employment program for adolescent mothers that offers on-the-job training in the summer and vocational education for health careers through Houston Community College.

Conclusion

We are failing to help young people make responsible decisions about sex, and we are neglecting the problems of teenage parents, especially young mothers. It makes sense, socially and financially, to pursue changes in policies and programs that can help youngsters lead their lives in more positive ways.

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Pelvic Ultrasonography 23

William L. Koontz and Richard Fellows

The diagnosis and management of female pelvic abnormalities in children and adolescents are among the most difficult problems in gynecology. The patient's family often is upset about the possibility of reproductive tract abnormalities, and the patient is apprehensive about the diagnostic and therapeutic procedures that may be used. Indeed, these procedures may have the potential to cause serious psychologic trauma.

High-resolution pelvic sonography has been extremely useful in the diagnosis and management of these problems. Not only does it have a high degree of accuracy in delineating many of these abnormalities, but it is both noninvasive and painless, making it an extremely suitable diagnostic technique in the evaluation of these patients.

It must be stressed, however, that while expert ultrasonography may be of great value in the diagnosis and management of female pediatric and adolescent pelvic problems, it still must be regarded as an adjunct to more traditional methods. The common tendency to request ultrasonography before a thorough history and physical examination and routine laboratory tests must be avoided.

Moreover, with the exception of some pregnancy evaluations, ultrasonography seldom is capable of making a definitive diagnosis. While it may be valuable in predicting the presence or absence of normal pelvic organs and the nature of any abnormalities, direct visualization and/or tissue diagnosis frequently are required for a definitive determination.

Physics and Instrumentation

Ultrasound is sound with a frequency above the range of normal human hearing (higher than 20,000 cycles per second). Diagnostic ultrasound is in the range of approximately 1–10 million cycles per second (MHz). Unlike x-ray, ultrasound is nonionizing and requires a medium for transmission. Its diagnostic use is based on recognition of the reflection of ultrasound when it passes through an interface to a tissue of different density. As the frequency of sound increases, the ability to resolve small distances increases while the ability to penetrate tissue decreases. Therefore, different frequencies are used for different indications.

The great majority of obstetric and gynecologic sonography done today is with either static or real-time gray-scale B-mode scanning, which results in a two-dimensional cross-section of the body area being scanned. Gray-scale imaging simply means that the intensity of the reflected sound is displayed as various shades of gray, brightness being proportional to the reflectivity of tissue interfaces. This technique allows a very precise characterization of tissues. In static scanning, a detailed "still" picture may be obtained, whereas real-time scanning allows visualization of motion such as fetal heart action. Real-time scanning may be done with transducers of either the linear array or sector types. Linear array transducers are appropriate when large areas are to be viewed; sector scanning often is used for examining small structures or

when it is particularly important to view the area behind the pubic symphysis.

Normal Anatomy, Scanning Techniques, and Limitations of Sonography

Scanning usually is done with the patient supine. It is imperative that she has a full bladder, the fluid-filled bladder not only providing an "acoustic window" through which the other pelvic structures may be more clearly viewed, but a landmark so that the anatomic relationships of abnormalities may be more accurately determined (Figs. 23-1 and 23-2).

In general a 3.5-MHz transducer is used for older children and a 5-MHz transducer for infants because more resolution is desirable and less penetration required in the small patient. Linear array real-time scanning usually is not preferred for small children because of the difficulty in directing the beam behind the pelvic symphysis.

The uterus can be identified sonographically in a female of any age. It is particularly easy to view the uterus in a newborn because it is relatively large due to the trophic effects of maternal estrogens during pregnancy.

Sonographic visualization of the pediatric vagina is, at best, difficult, and an accurate diagnosis of abnormalities usually is not possible because the normal vagina is a collapsed "potential cavity." The diagnosis of vaginal abnormalities usually is better done by direct examination and visualization, under anesthesia if necessary.

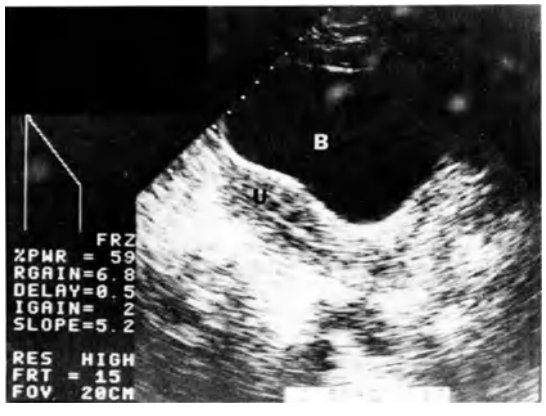

Figure 23-1. Transverse scan of pelvis with adequately filled bladder. Note easily visualized uterus somewhat deviated to the patient's left. *B* bladder; *U* uterus.

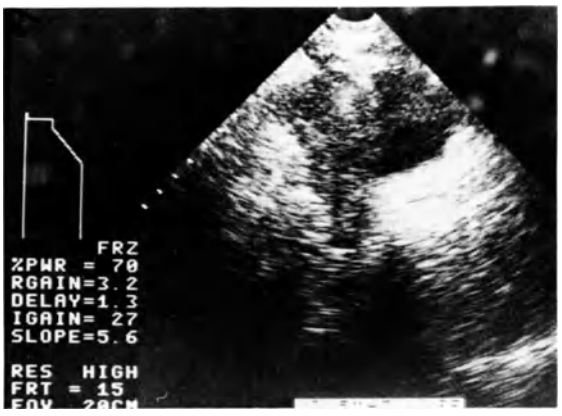

Figure 23-2. Transverse scan of pelvis with empty bladder. Note that no pelvic structures can be clearly identified. This underscores the importance of a full bladder for adequate pelvic sonographic examinations.

Although the ovaries may be difficult to evaluate sonographically in the child under 2 years, an accurate assessment of their presence, size, and acoustic character usually can be made in the older child (Fig. 23-3). Distortion of the normal pelvic anatomy by pelvic masses (including pregnancy) may make it impossible to visualize the ovaries.

With rare exceptions, normal fallopian tubes cannot be evaluated well with ultrasound. However, when they are abnormally distended they often can be clearly identified.

Indications

Indications for sonography of the pelvis in the pediatric or adolescent patient may be listed as follows: (1) primary or secondary amenorrhea; (2) precocious puberty; (3) ambiguous or anomalous genitalia; (4) pelvic mass; (5) diagnosis and evaluation of pregnancy; and (6) pelvic pain. The remainder of this chapter will be devoted to discussing in detail each of these clinical situations.

Primary Amenorrhea

Primary amenorrhea should be investigated when a girl fails to begin menstruating by age 16, particularly when there is no obvious abnormality that would have led to earlier investigation.

For most cases of primary amenorrhea, sonography's main value is that it demonstrates the presence of normal-appearing internal reproductive organs, particularly the ovaries. Subsequent endocrinologic and genetic testing will define the nature of the problem. When normal internal organs are not seen sonographically, valuable diagnostic clues may be obtained, but a definitive diagnosis almost always requires more direct techniques such as laparoscopy or laparotomy. Any abnormal tissues such as streak gonads should be biopsied.

In the absence of symptoms other than amenorrhea, all abnormalities except for absent or rudimentary ovaries rarely are detected by a routine pelvic exam. When there are additional signs and symptoms (cervix not visualized, pelvic mass), obstructive abnormalities of the cervix and vagina may be diagnosed by the sonographic demonstration of a grossly dilated endometrial cavity, with or without dilated fallopian tubes.

In complete vaginal obstruction such as with an imperforate hymen the bulging, sonolucent proximal vagina may be visualized along with the enlarged uterine cavity.[1]

Secondary Amenorrhea

Pregnancy is by far the most common cause of secondary amenorrhea. Haller et al found that intrauterine pregnancy was the diagnosis in more than 60% of their series of pelvic sonograms in 350 patients under 16.[2]

Precocious Puberty

The majority of precocious puberty in females is idiopathic or constitutional in etiology. Although pelvic sonography is unlikely to aid in the evaluation of patients with precocious puberty, it may be of value in detecting estrogen-producing ovarian tumors, which are responsible for a small percentage of these cases.

Ambiguous or Anomalous Genitalia

Few medical problems are as emotionally difficult as the birth of a child with ambiguous or anomalous genitalia. A rapid and accurate assessment of the problem is desirable. Unfortunately, sonography is often not of great value here. Probably its most worthwhile use is in identifying normal female internal genitalia in cases of female pseudohermaphroditism due to congenital adrenal hyperplasia. Even this may be difficult to accomplish until the child is older.

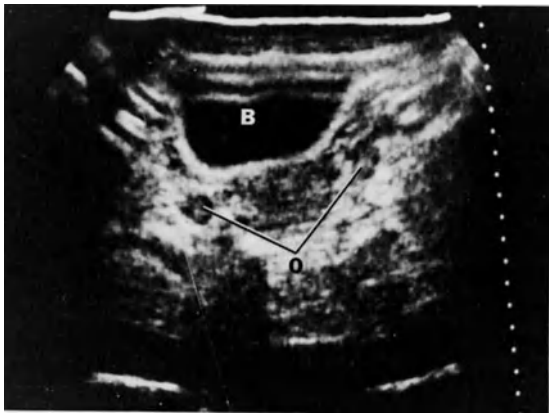

Figure 23-3. Transverse scan of pelvis demonstrating normal ovaries. This view is made possible because of the "window" provided by the full bladder. *O,* ovaries; *B,* bladder.

Pelvic Mass

The differential diagnosis of pelvic masses in infants includes distended urinary bladder, presacral meningocele, presacral teratoma, and hydrometrocolpos. Sonography may be of help in differentiating these diagnoses. The diagnosis of hydrocolpos is suggested by a cystic pelvic mass low in the midline that contains cellular debris (Fig. 23–4).[3] This is a

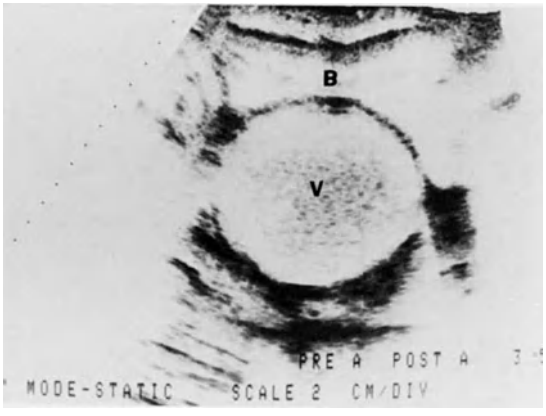

Figure 23-4. Transverse scan of pelvis demonstrating the distended vagina of hydrocolpos. This case resulted from an imperforate hymen. *B,* bladder; *V,* vagina.

particularly important preoperative diagnosis because if the condition is not recognized inappropriately extensive surgery such as a hysterectomy may be done.

Pelvic masses in children past infancy are rare. Most ovarian enlargements in the pediatric age group are nonneoplastic follicular cysts. These usually are asymptomatic unless torsion or infarction occurs, producing acute pain.

Benign cystic teratoma is the most common neoplastic ovarian enlargement in all pediatric age groups. Presenting symptoms usually are abdominal enlargement and/or pain secondary to torsion or intraperitoneal leakage of cyst contents. It should be kept in mind that in younger children the tumor is more frequently located in the abdomen rather than the pelvis.[4] An accurate preoperative diagnosis may be very difficult without sonography, particularly when pain is the presenting symptom.

A classic sonographic picture of cystic teratomas with a solid area projecting into a predominantly cystic mass has been described.[5] However, large series describing sonographic findings in proven cases of teratoma have shown that the ultrasound picture may be highly variable.[6,7] Moreover, Laing and associates found that almost one-fourth of the masses in their series of teratomas were not visible sonographically.[7] In summary, sonography may help in the preoperative diagnosis and evaluation of benign cystic teratoma but, as with other masses, it is not definitive (Fig. 23-5).

An interesting finding in Haller's series of pelvic sonograms in pediatric patients was that about one-half of the girls referred for suspected pelvic masses had normal sonograms.[2] In these cases, the initial use of ultrasound prevented the use of unnecessary radiographic examination or invasive diagnostic procedures.

Sonography also may be valuable in the diagnosis of abdominal enlargement caused by abnormalities not in the reproductive tract, such as polycystic kidneys.

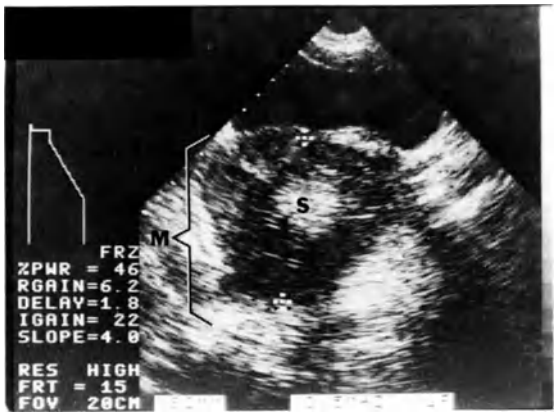

Figure 23-5. Transverse scan of pelvic mass which proved to be a benign cystic teratoma. Note central echoes suggesting solid components. *M*, mass; *S*, solid components; *B*, bladder.

Diagnosis and Evaluation of Pregnancy

Pregnancy will be the most common diagnosis in any series of pelvic sonograms in females of reproductive age. Pregnancy accounted for 60% of the diagnoses in the series of more than 350 pediatric sonograms reported by Haller et al.[2] Their youngest pregnant patient (9 years old) had never menstruated.

The possibility of pregnancy is one of the most compelling reasons for the use of sonography as the primary method of evaluating pelvic masses in this age group. Sonography certainly should be done before resorting to radiography or invasive procedures that could adversely affect early pregnancies.

Many pelvic sonograms will be done on adolescent females as part of an evaluation prior to elective abortion. It is especially important to accurately diagnose and date the pregnancy with ultrasound since these patients often have an uncertain menstrual history. Accurate pregnancy dating is essential before the appropriate abortion technique can be chosen or for determining that the pregnancy is too far advanced for safe and/or legal termination. Accurate pregnancy dating also is beneficial in evaluating pregnancies for fetal growth abnormalities, which are much more likely in adolescents than in older mothers.

One rule stands out in the sonographic determination of gestational age: the earlier, the better. Unfortunately, many adolescents do not present early in pregnancy. Ideally, each institution should generate its own data on sonographic fetal measurements to date

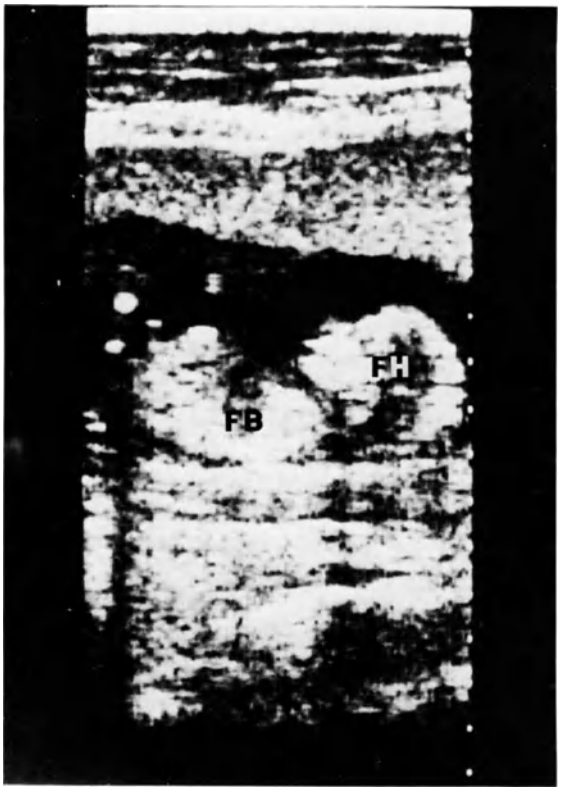

Figure 23-6. View of fetus suitable for measurement of crown-rump length. *FH*, fetal head; *FB*, fetal body.

pregnancies. If this has not been done, composite data or curves generated from similar patient populations should be used.

Usually, intrauterine pregnancies cannot be identified sonographically prior to the end of 5 weeks of amenorrhea, after which an intrauterine gestational sac may be seen. Enlargement of the gestational sac is the main ultrasonic feature of pregnancy from 5 to 7 menstrual weeks, with fetal motion usually identifiable after 8 weeks. Fetal crown-rump length is measurable by 9 weeks and is the most widely used sonographic parameter of fetal age in the first trimester (Fig. 23-6). Although some investigators have had success using biparietal diameters to date first-trimester pregnancies, this measurement is not widely used until after 14 weeks of gestation.[8] Because of fetal motion, crown-rump length is very difficult to measure with static scanning equipment. However, Nelson has demonstrated that real-time sonographic measurement of fetal crown-rump length is both easily obtained and accurate in the dating of early pregnancy.[9] The technique of measuring crown-rump length is easily mastered and involves measuring the maximum distance between the two fetal poles, excluding the extremities. Several measurements should be taken to ensure that the full length is seen. In the absence of self-generated norms, Nelson has suggested that the uncorrected regression analysis values in Robinson's study have a high degree of accuracy.[9,10] The crown-rump length measurement taken between 8 and 14 weeks is accurate to within 4 to 7 days.[8,10,11]

Measurement of the fetal biparietal diameter (BPD) was the first sonographic fetal measurement used to date pregnancies and is unquestionably the most commonly used (Fig. 23-7). It usually is easily measured after 14 weeks of gestation. Sabbagha and Hughey have demonstrated that BPD values obtained with real-time sonography are not significantly different from those obtained with static

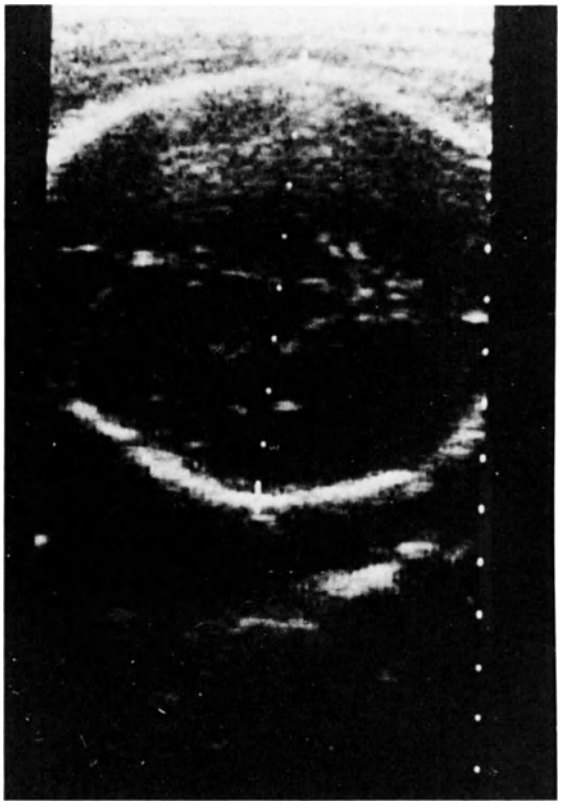

Figure 23-7. Demonstration of the plane in which the fetal biparietal diameter is measured. Note the incomplete midline echo and the symmetry of the fetal head. The measurement is taken from the outside of the near (top) edge to the inside of the far (bottom) edge.

equipment.[12] They also have devised a composite chart of BPD vs. gestational age that has been widely accepted as a standard. It is suggested that this chart be used if individual norms have not been developed.

Although the accuracy of BPD in determining gestational age is quite good in early pregnancy, it is not always a good indicator in later pregnancy. This is not because the measurement itself is inaccurate, but rather because of variations in the growth patterns of individual fetuses in later pregnancy. After 28 weeks of gestation, a BPD determination is accurate only to a range of 6 weeks. It should, therefore, be stressed that gestational age in late pregnancy cannot be pinpointed with sonographic measurement of the BPD.

Although the technique for obtaining accurate BPD measurements is relatively straightforward, it does require some experience. The plane of measurement is now well standardized.[13] Some difficulty may be encountered in early pregnancy because of fetal movement, especially if static scanning is used. In addition, a reliable measurement may be difficult to obtain if the head is deep in the maternal pelvis, thereby preventing the transducer from being placed at the proper angle to the fetal head.

Recently, there has been great interest in sonographically measured fetal limb lengths and their relationship to gestational age. The femur is most commonly measured, although tables exist for all long bones (Fig. 23-8). Several carefully derived tables have been published.[14–16] Seeds and Cefalo have demonstrated that there is extremely close correlation among the various studies of fetal femur length.[17] They believe that composite limb standards are of little benefit, and that any of the well-done studies may be used.

Although most novice sonographers approach femur length measurement with some apprehension, the technique is simple and yields very reproducible values. It is particularly valuable when the BPD is difficult to obtain such as when the fetal head is deep in the pelvis. Fetal femur length measurements appear to be as accurate as BPD in predicting gestational age early in pregnancy and may be considerably more accurate (less subject to individual variation) in the third trimester.

It is important to detect intrauterine growth retardation (IUGR), a common complication in adolescents. The sonographic diagnosis of IUGR usually is dependent on a precise knowledge of gestational age. Sabbagha has reviewed the diagnosis of IUGR with serial sonographic BPD measurements alone and has discussed the problems with this method.[18] Currently, most investigators use a combination of fetal measurements in evaluating a fetus for possible IUGR. These most often include BPD or head circumference, abdominal circumference, and femur length.[19,20] Various combinations of measurements have been used to sonographically estimate fetal weight in utero, and these techniques may be of value in following fetuses at risk for IUGR.[21] The presence of oligohydramnios may serve as a valuable warning sign of IUGR, but as a routine screening parameter lacks both specificity and sensitivity.[22] The measurement of total intrauterine volume is a fairly accurate parameter for diagnosing IUGR, but the procedure is tedious and requires static scan-

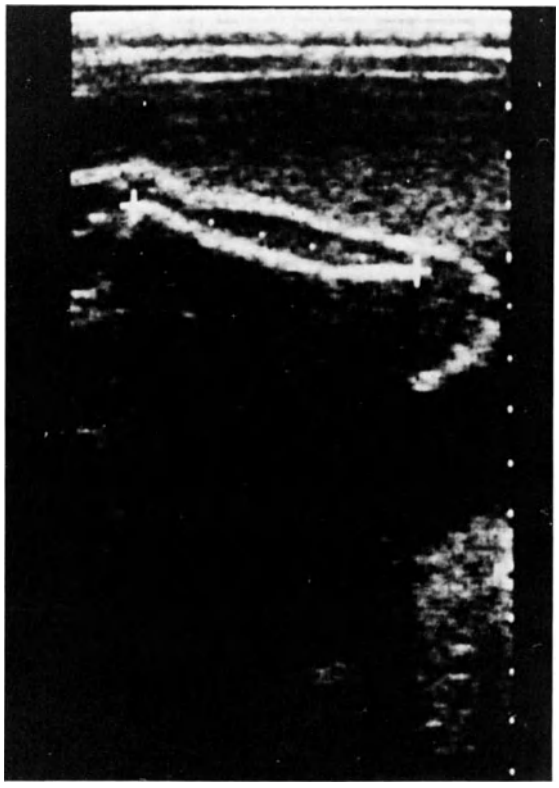

Figure 23-8. Demonstration of measurement of fetal femur length. Note the uniform appearance of the full length of the bone.

ning equipment.[23] Also, the grading of placental maturity with sonography may provide a clue to the presence of IUGR, but this technique is not accurate enough to be used alone.[24]

Other than pregnancy dating, obstetric ultrasound is most widely used for detecting fetal anomalies. This is particularly important in adolescent pregnancies because of what are often poor social circumstances. In these cases, the pregnant girl and her family need as much accurate information as possible so that they may make fully informed decisions.

Although a precise diagnosis of fetal anomalies often requires sonographers with extensive experience in developmental anomalies, we find that many problems are picked up on initial scans done by community ultrasonographers. Generally, the ultrasonographer in the community hospital recognizes that something is abnormal and refers the patient to a medical center for further evaluation. Many of the referral diagnoses are accurate. It should be stressed, however, that if the patient is known to be a high risk for a fetal abnormality that may be detectable by ultrasound, she should be scanned by a sonographer with the skill and experience to adequately evaluate the problem.

Abnormalities of virtually all fetal organ systems have been detected with sonography, and the list of prenatally diagnosed anomalies continues to grow.[24,25] The most familiar prenatal diagnoses made with ultrasound are hydrocephalus, anencephaly, large neural tube defects, abdominal wall defects, gastrointestinal atresias, and urinary tract abnormalities (Figs. 23-9 and 23-10). Any gross abnormality in these areas usually can be readily detected by community ultrasonographers. Most of these patients should then be referred to tertiary care centers for further study.

Increasing experience and sophistication have led to the sonographic diagnosis of cleft lip and palate, complex cardiac malformations, and many other anomalies that were until recently undetectable.[26,27] With further experience, the use of sonography for diagnosing and evaluating fetal abnormalities will undoubtedly continue to increase.

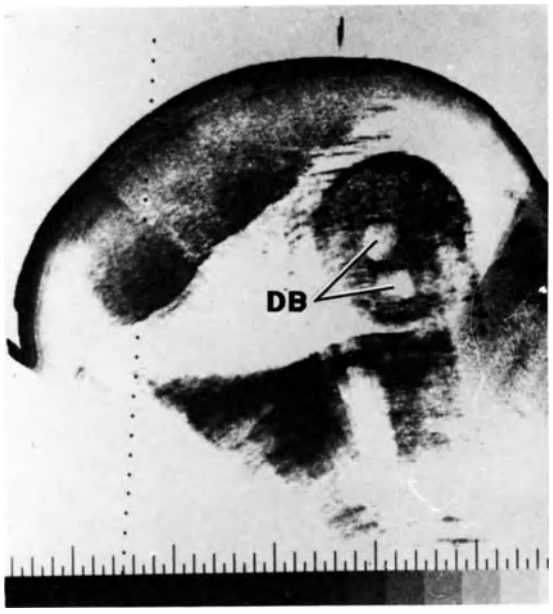

Figure 23-9. Cross-section of fetal abdomen demonstrating classic "double-bubble" sign of duodenal atresia. *DB*, double bubble.

Evaluation of Pelvic Pain

Pelvic pain is one of the most common reasons for gynecologic consultation in the pediatric or adolescent patient. Although sonography usually is of limited help in the workup of pain when there is a normal physical examination, it may be valuable in detecting pelvic masses and pelvic fluid collections.[28,29]

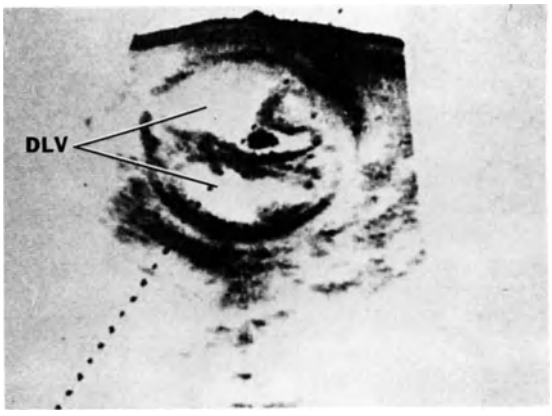

Figure 23-10. Cross-section of fetal head demonstrating severe hydrocephalus. Compare with normal anatomy in Fig. 23-7. *DLV*, dilated lateral ventricles.

Pelvic ultrasound may be of great value when the differential diagnosis of pelvic pain includes ectopic pregnancy. The role of sonography in these cases is primarily to demonstrate an intrauterine pregnancy, as the incidence of combined pregnancy (ectopic and intrauterine pregnancies both present) is extremely low.[30] Although early experience with sonography in evaluating possible ectopic pregnancies was somewhat confusing because the normal appearance and location of the gestational sac was not known, further experience has eliminated most of this confusion.[31] It is now known that most gestational sacs are placed eccentrically, while the pseudogestational sac consisting of early decidua is in the midline of the uterus.[32] Of course, the recognition of a more advanced intrauterine pregnancy, or the presence of a gestational sac or fetus in the adnexa, makes the correct diagnosis obvious.

Various schemes involving a combination of sonography and a serum or urine pregnancy test have been proposed.[33] In general, the absence of an intrauterine pregnancy upon sonographic examination along with a positive pregnancy test should make the clinician highly suspicious of an ectopic pregnancy.

Summary

Ultrasound often is invaluable in the evaluation of gynecologic and obstetric problems in pediatric and adolescent patients. The technique is not, however, a substitute for meticulous histories and physical examinations. Sonography generally is quick, noninvasive, and devoid of psychologic trauma. When used within the scope of its limitations and those of the examiner, ultrasound often aids in the management of these patients.

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The Adolescent Athlete 24

Mona M. Shangold and Gabe Mirkin

Benefit of Exercise for Children

Adolescent girls today, unlike their predecessors, are being encouraged to exercise—and rightfully so. The inactivity of previous generations has shown that a sedentary lifestyle promotes osteoporosis,[1] cardiovascular disease, and obesity, the latter of which increases one's risks of developing diabetes mellitus, gallbladder disease, and breast and endometrial cancers. A girl who exercises regularly can expect lifetime benefits.

Exercise can be encouraged by teaching girls to enjoy physical exertion. Unfortunately, parents sometimes become overly enthusiastic, and the adolescent rebels by refusing to participate. Many well-meaning coaches have encountered the same failures. If adolescents are to accept exercise as an essential component of life and incorporate it into their routine, they, not others, must be the motivating factor behind their decision to participate.

Endocrine Changes with Exercise and Training

Studies of adult women have shown that levels of several protein and steroid hormones rise during exercise, but the long-term effects of these transient changes remain to be demonstrated. Similar changes would be expected in adolescents. Peripheral concentrations of estradiol,[2] progesterone,[2] and testosterone[3] rise during exercise and return to normal within an hour or two after the person stops exercising. Although hyperprolactinemia and hyperandrogenism can promote menstrual dysfunction, exercise has not been proven to cause sustained elevations in the baseline levels of either.

The prevalence of oligomenorrhea among postmenarchal athletes (10–20%) is higher than that among the general population (5%).[4,5] These figures make it tempting to blame exercise, but since many factors change simultaneously during the course of a conditioning program, it is difficult to pinpoint causality. Weight loss and the loss of body fat usually occur during a conditioning program, and these factors may lead to amenorrhea even in the absence of exercise.[6,7] Low-level weight or body fat may also lead to amenorrhea,[8], and women who exercise regularly may have such levels.

In addition to the loss of weight and fat, female athletes have long-term alterations in baseline hormone levels, as well as changes in diet, sleep, and physical and emotional stress. Any or all of these variables may contribute to menstrual dysfunction. Lower baseline progesterone levels in the mid-luteal phase of the cycle and shortening of the luteal phase correlate with increased mileage for female runners.[9] This, however, appears reversible, resolving as the runner reduces her mileage.[10]

The multifactorial nature of these menstrual changes has been shown in ballerinas, who have menstruated regularly during times of inactivity at low levels of weight and body fat,

yet have stopped menstruating when they resumed their usual activity.[11]

Menarcheal Delay

Athletic girls tend to begin menstruating later than nonathletes.[12,13] It is not clear whether exercise delays menarche or menarcheal delay promotes athletic success. Some researchers believe that strenuous physical activity prior to puberty actually delays menarche.[8,14,15] It is equally plausible, however, that delayed puberty promotes athletic success and perseverance. At puberty, higher estrogen levels lead to epiphyseal closure and fat deposition, factors which generally are not conducive to athletic success. Thus, earlier menarcheal age is associated with shorter adult height.[16] It cannot be assumed, of course, that tallness and thinness enhance athletic success, since many factors contribute to athletic skill. Tall and thin athletes may have an advantage in some sports, but genetic endowment, proper training, and continued discipline are also required for success.

It is probable that the association between exercise and menarcheal delay involves causal contributions by both factors—i.e., prepubertal exercise may delay menarche by promoting thinness and delaying the critical body composition needed to trigger puberty, and menarcheal delay may promote athletic success and perseverance by postponing epiphyseal closure and fat disposition.

Any girl who has not begun to menstruate by the age of 16 should have a thorough physical examination, which should include a pelvic evaluation. Fourteen-year-olds who have not begun to develop breasts or axillary or pubic hair also should be examined. Physical findings, in both cases, dictate whether further evaluation is warranted.[17] There is no reason for any girl to refrain from exercising while undergoing evaluation, nor should fear of pubertal delay discourage her from exercise. Constitutional delay of puberty in an athlete requires no treatment and no change in lifestyle. However, it is dangerous to attribute delayed puberty to exercise without thorough evaluation because serious pathology can easily be overlooked (see chapter 11).

Oligomenorrhea

Postmenarcheal athletes should be examined if menses occurs more often than every 20 days, or less than every 60 days, or if an adolescent athlete with a history of regular menses does not bleed for 3 months. If physical examination reveals normal secondary sexual development without any unusual stigmata (e.g., short stature, webbed neck, cubitus valgus) and the pelvic examination reveals a vagina and uterus, further evaluation depends on the preference of the patient and her family. Oligomenorrhea is common among teenagers, and significant causative pathology is uncommon in this age group. The incidence of significant causative pathology is greater in those age 20 and older, and warrants thorough evaluation.

Several options exist for oligomenorrheic athletes who are under age 20. Some may prefer thorough evaluation and subsequent treatment; some may prefer thorough evaluation and subsequent observation if tests are normal. Still others may prefer only observation without either evaluation or treatment. Obviously, hyperprolactinemia, hyperandrogenism, hypothyroidism, and hypergonadotropism (premature ovarian failure or resistant ovary syndrome) require further evaluation and appropriate therapy. If none of these conditions is found, euestrogenic athletes (i.e., those with estrogenic cervical mucus) may be treated with a 5- or 10-day course of medroxyprogesterone acetate (10 mg daily) to induce withdrawal bleeding, which confirms their euestrogenic status. Induced withdrawal bleeding every 30 or 60 days is appropriate for these adolescents and may prevent the heavy, infrequent bleeding that often occurs. It is not necessary to treat euestrogenic adolescents who bleed spontaneously more often than every 60 days unless the problem continues past the age of 20 or bleeding episodes are heavy and contribute to anemia. Chronic, unopposed estrogen in due time may lead to endometrial hyperplasia and adenocarcinoma.However, this is unlikely if the anovulatory condition has lasted less than 5 years. Thus, it is reasonable to treat those euestrogenic, anovulatory athletes who experienced menarche 5 or more years ago, but to defer treatment in others until 5 years after men-

arche. It is equally acceptable to treat patients who request therapy. Any woman who has had chronic anovulation for more than 5 years should be treated with a 10-day course of medroxyprogesterone acetate (10 mg daily) at monthly intervals.[18]

Hypoestrogenic athletes (i.e., those lacking good cervical mucus) may be treated with cyclic estrogen-progestin therapy monthly. This therapy is optional and probably unnecessary for teenagers. After age 20, such athletes should be treated with monthly conjugated estrogens (0.625 mg daily on the first 25 days of every calendar month) and medroxyprogesterone acetate (10 mg daily on days 16–25 of estrogen therapy) for skeletal and urogenital protection. Those who require contraception may be treated with low-dose ($\leq$ 35 μg estrogen) oral contraceptives instead. While serious athletes under age 20 are highly unlikely to request ovulation induction for immediate fertility, such a patient should be evaluated and treated with the same protocol that would be followed for any older athlete.

Oligomenorrheic and amenorrheic athletes should be reexamined yearly regardless of whether they are being treated or observed. If the condition persists after the athlete turns 20, thorough evaluation and initiation of therapy are appropriate.

Dysmenorrhea in Athletes

Dysmenorrhea is caused by prostaglandin-induced myometrial contractions and generally indicates normal ovulatory function. While some athletes have less discomfort during exercise and some report improvement since they have begun exercising regularly, exercise alone rarely brings total relief. Following a pelvic exam, dysmenorrhea should be treated with prostaglandin synthetase inhibitors (see chapter 12).

Contraception in Athletes

Any adolescent athlete who wants contraception should be examined before it is prescribed. Those who have regular menses may use oral contraceptives (containing 30–35 μg estrogen per tablet) or barrier methods if they are reliable and motivated. Oligomenorrheic and amenorrheic athletes may also select either option after appropriate evaluation. Intrauterine contraceptive devices are not recommended for women who may someday wish to have children because of the small risk of pelvic infection, which may impair future fertility.

Pelvic Examination

Any adolescent athlete who is concerned enough to ask about menstrual problems or who requests a pelvic examination deserves one for reassurance if for no other reason. No girl is too young to have a pelvic examination. The first one, however, should be accompanied by an explanation of what exactly is being done, why, and how it will feel (see chapter 4). No normal female should be expected to cooperate and relax during a pelvic exam unless the procedure is thoroughly explained.

Hematologic and Coagulation Changes with Exercise

Regular training leads to expansion of the intravascular volume, including an increase in plasma that is greater than that of red blood cell mass.[19] This dilution often leads to a pseudoanemia that is of no consequence. However, approximately 40% of women of reproductive age are iron deficient,[20] even though only a small proportion are truly anemic. This iron deficiency is caused by a combination of inadequate iron intake and iron loss during menstruation. Even in the absence of anemia, deficient iron stores can impair lactate clearance and athletic performance.[21] Adolescents are even more prone than adults to nutritional inadequacies. Thus, it is reasonable to recommend supplementary iron for teenagers.

Regular training also leads to decreased thromboembolic risks. High density lipoprotein (HDL) cholesterol concentrations in adult marathon runners are greater than those in control groups.[22] HDL levels increase with physical activiy,[23] and in adults are associated with some protection against ischemic heart disease.[24] Exercise also helps in the prevention of cardiovascular disease by enhancing the

fibrinolytic activity that occurs in response to venous occlusion.[25] This effect is most pronounced in women, in individuals with low initial levels of stimulated fibrinolysis, and in those with low initial levels of cardiovascular fitness. These data demonstrate reduced cardiovascular and thromboembolic risks in women by more than one mechanism. Since such risks are low in adolescents, these changes are less important than in later life.

Athletic Competition with Boys

Girls and boys can exercise together and compete on equal terms prior to puberty, which generally begins at an earlier chronologic age for females than for males. Pubertal girls' higher estrogen levels promote fat deposition and epiphyseal closure. The exact mechanism of epiphyseal closure is not understood; however, it may be associated with local formation of estrogen in bone marrow.[26] Higher androgen levels in pubertal boys promote muscle formation and long bone growth. As a result, postpubertal males tend to be taller and more muscular than postpubertal females, giving males an athletic advantage.

Musculoskeletal Injuries

A major concern about children's vigorous exercise is that injuries may have long-lasting effects on growth and development. One of the leading authorities on this subject is Lyle Micheli, M.D., who has investigated this problem extensively and described a number of risk factors that predispose children to overuse injuries.[27] Such injuries often result from improper training, musculotendinous imbalance, anatomic malalignment of the lower extremities, improper footwear, unfavorable playing surfaces, and underlying musculoskeletal diseases. With the exception of apophyseal injuries (injuries to the tendon where it inserts over a growth plate), children are not any more likely than adults to develop athletic injuries.[28] In fact, anecdotal evidence from children's coaches implies that they are far less likely than adults to be injured while running long distances.

It has recently been observed that microtrauma can occur even in young children who run long distances. However, the long-term effects of such repetitive injury remain unknown. Other sports and shorter-distance running are not sources of concern for skeletal injuries and generally are considered safe.

A major concern about children's long-distance running is that vigorous exercise may damage their epiphyses, the growth plates of the long bones. As long as the epiphysis is open, a bone has the potential to continue growing. An open epiphysis can be demonstrated radiographically by its lack of calcification. In this case, the end of the bone (the epiphysis) will appear to be separated from the main part of the bone by an empty space called the epiphyseal cartilage. Prior to epiphyseal closure, the growth center is weaker than the rest of the bone and is more susceptible to fracture when subjected to excessive force. Several studies have shown that epiphyseal stress fractures occur rarely and seldom interfere with a child's ultimate bone growth.[29] Stress fractures (superficial cracks) in the major portion of the foot, leg, or pelvis are common running injuries. However, there is no evidence that young children are at increased risk of developing stress fractures or that stress fractures interfere with a child's ultimate growth.[30]

Nutrition for Athletes

Exercising children require more calories than sedentary ones. However, the nutritional requirements are about the same whether they are at rest or exercising. Exercise increases requirements for niacin, thiamin, pantothenic acid, and riboflavin, but adequate amounts will be provided if a balanced diet that contains sufficient calories is consumed. Milk, meats, and whole grains each contain all four "energy" vitamins. Children require smaller amounts of most nutrients than adults, largely because they weigh less. In most cases, a child who satisfies her hunger will eat enough calories to meet the needs of both exercise and normal growth. Height and weight increases should be plotted on growth curves as described by Stuart and Meredith.[31,32]

Cardiovascular Fitness

To attain cardiovascular fitness, children should sustain a heart rate of at least 140 beats per minute for at least 10 minutes in at least three exercise sessions per week—the same guidelines recommended for adult cardiovascular fitness.[33] Children who train this way can make significant gains in aerobic capacity, although the traditional measurements of maximal oxygen uptake do not reflect this.[34] Presumably, the active lifestyles of most children lead to a high threshold for improvement in maximal oxygen uptake, which may be an inappropriate measurement to follow for this age group. The fact that submaximal heart rates decrease significantly in children who train at submaximal levels confirms that training does have its effects.[34]

Endurance

Preadolescent girls can run long distances almost as fast as boys. The world record for the 1500-meter run for 10-year-old girls is 4 minutes 52 seconds, just 15 seconds short of the boys' record. However, the gap widens after puberty when the increased production of testosterone makes males stronger and faster. For example, the world record for an 18-year-old boy is 3 minutes 42 seconds, 38 seconds faster than the record for girls.

Adolescent girls and boys can use the same training methods.

Flexibility

Flexibility training is best achieved through slow, controlled motions that attempt to increase the range of joint motion. Training to accommodate the specific movements of a particular sport decreases the likelihood of injuries.

Strength Training

Both prepubertal and postpubertal weight training can lead to gains in strength. Maximal strength training is usually done by lifting the heaviest weight possible in a series of repetitions that lasts 30–50 seconds. A very heavy weight usually can be lifted and slowly lowered 8 to 12 times during that period. However, strengthening a muscle requires a person to lift a near-maximal load. If the force on a bone exceeds its inherent strength, it will break at its weakest point—its epiphysis.

Because of the danger of breaking their uncalcified epiphyses, preadolescents should not do maximal strength training. However, they can gain both strength and coordination by lifting lighter weights in sets of more than 12 repetitions. Within a year of pubertal onset, however, the growth centers of most bones are closed, so a girl can do maximal strength training without increasing the chance of injury.

Conclusion

Adolescent athletes should know the benefits of exercise and be encouraged to begin exercising early in life. Although menarcheal delay is common among athletes, there is no evidence that it is harmful. Any postmenarcheal reproductive problems, however, should be evaluated and treated. Most reproductive problems associated with exercise are reversible and normal fertility can be expected, although therapy may be required.

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Dermatologic Problems 25

Melissa L. F. Knuckles and Lafeyette G. Owen

The skin is an integral part of the body, and also has special independent functions. The outer part of the epidermis contains keratin which is a resistant protein barrier and protects against the outer environment. The dermis contains numerous blood vessels, nerves, and lymphatics which are in close relation with the viscera beneath, and allow the organism to adjust to changes in the outer environment. Changes in the integument may indicate a localized disease process or may be indicative of a systemic process.

Dermatitis

Atopic Dermatitis

This chronic skin disorder is of unknown etiology. Hereditary, allergic, environmental, and psychogenic factors are signficant. It can affect any age. Bilateral lesions prominant in the flexural areas are common. The lesions are erythematous papules and plaques with a slight scale. Lichenification, excoriation, secondary pyogenic infection, and pruritus are characteristic (Fig. 25–1). Measures to reduce all aggravating factors should be used. Infrequent bathing, antihistamines, and lubrication with bath oils and lotions as well as topical steroid preparations are effective. With secondary infection, broad spectrum antibiotics should be used. Temporary use of systemic corticosteroids in extremely pruritic, inflammatory cases is indicated.[1]

Lichen Simplex Chronicus (Localized Neurodermatitis)

Neurodermatitis is a circumscribed form of eczema (dermatitis) caused by repeated scratching and rubbing. Psychogenic factors are significant. It is more common in females and is characterized by lichenified, scaly skin found most commonly on the posterior neck, inner thighs, and legs. Anal and genital pruritus often coexist. Prurigo nodularis is a condition in which nodules develop at sites of repeated excoriations. Topical corticosteroids, lubricating agents, and antihistamines are indicated. Intralesional triamcinolone (4 mg/ml) for nodules is effective.

Figure 25-1. Atopic dermatitis.

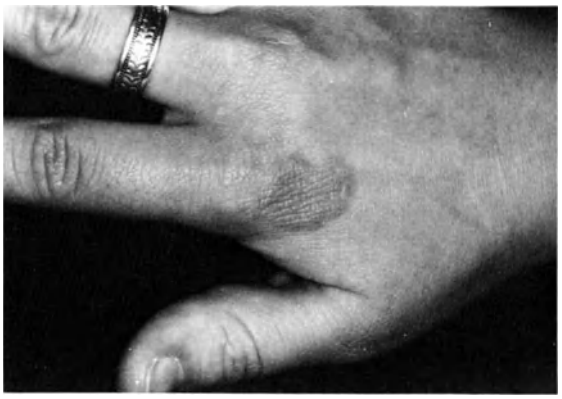

Figure 25-2. Fixed drug eruption.

Fixed Drug Eruption

The primary lesion due to ingestion of a drug is a hyper-pigmented macule with occasional vesiculation (Fig. 25-2). With readministration of the drug, the pigmented areas will reactivate. The neck, hands, and genitals are the sites of predilection. Phenolphthalein, tetracycline, anticonvulsant drugs, and tranquilizers are the most causative agents. Therapy consists of discontinuance of the offending agent.

Contact Dermatitis

This is caused by reactions to primary irritants or sensitizing agents which will produce a dermatitis only on skin allergic to a specific substance (type IV–delayed hypersensitivity reaction).[2] Any exposed part of the body may be affected. Vesicular, erythematous, edematous lesions in patches or linear streaks are characteristic. Secondary pyogenic infection may be present. The most common types are as follows:

1. Linear areas of vesiculation caused by plant sensitivity, primarily from the *Rhus* species (poison ivy).
2. Periorbital edema and dermatitis secondary to nail polish and eyelash curlers.
3. Facial dermatitis due to cosmetics.
4. Crusted, lichenified skin in any area of contact with nickel: jewelry, belt buckles, zippers, or glasses.
5. Contact dermatitis of the trunk due to elastic in waistbands or underwear.
6. Genital dermatitis due to contraceptive gels and creams, douching agents, underwear, and condoms.
7. Hand eczemas caused by detergents or soaps which act as irritants (not sensitizers).

Therapy is to eliminate the offending agent. Topical corticosteroids and antihistamines are helpful in mild cases. With acute processes, warm water soaks plus short-term systemic steroids may be warranted.[2]

Seborrheic Dermatitis

Seborrheic dermatitis in its simplest form is known as dandruff (seborrhea). Seborrheic dermatitis may also occur on the eyebrows, ears, nasolabial folds, axillae, anterior chest, and pubic area. The scale of seborrhea is somewhat greasy and the disorder may be somewhat pruritic. The etiology is unknown, but the condition is aggravated by cool, dry weather and emotional stress. Nonfluorinated topical corticosteroids and shampoos containing tar are very helpful.

Pauplosquamous Diseases

Psoriasis

Psoriasis is a chronic disease of unknown etiology in which epidermal turnover is greatly increased. It appears to be hereditary and may be associated with rheumatoid arthritis. Stress, hormonal factors, environment, alcohol, and pregnancy influence the disease process. Guttate (droplike) psoriasis occurs most commonly in adolescents, following a streptococcal infection. The primary lesions are well-defined, beet-red papules or plaques with a silvery-white scale (Fig. 25–3). If the scales are removed, bleeding points are exposed (Auspitz's sign). Trauma leads to the development of new lesions (Koebner's phenomenon). The most common sites are the scalp, elbows, knees, nails, and genitalia. The nails are often pitted and show onycholysis (separation of the nail from the nailbed) (Fig. 25–4). The differential diagnosis includes seborrheic dermatitis, secondary syphilis, lichen planus, pityriasis rosea, and fungal infections. Therapy consists of treatment with tar prep-

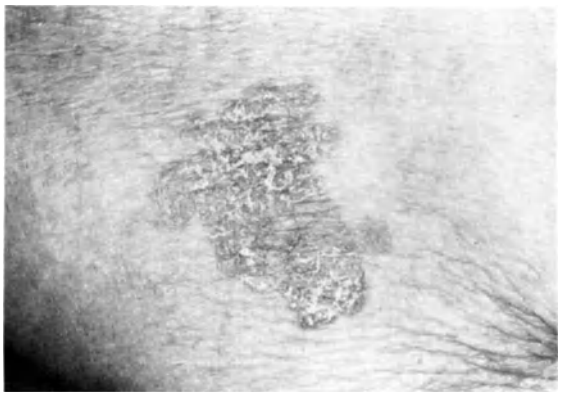

Figure 25-3. Psoriasis.

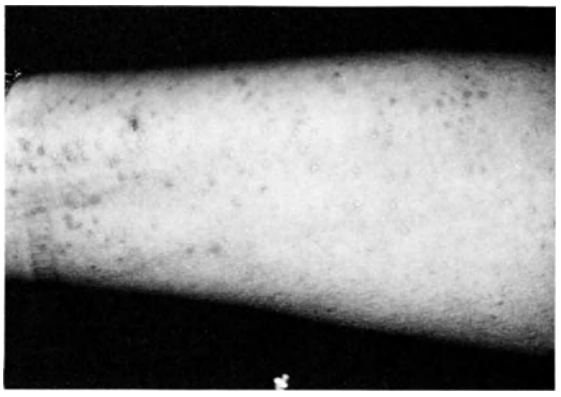

Figure 25-5. Lichen planus.

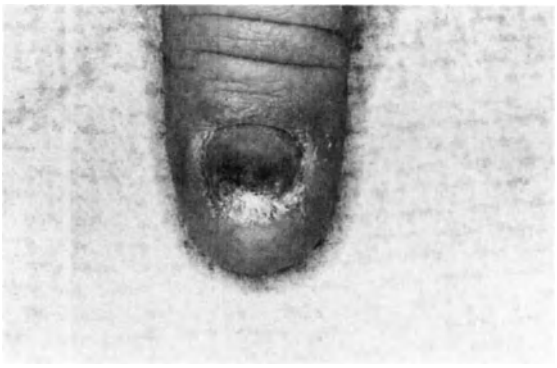

Figure 25-4. Psoriasis.

arations, topical corticosteroids, and ultraviolet light. The Goeckermann technique (tar and UVL) is very effective in moderately severe psoriasis.[3]

Antihistamines and lubricating oils with or without tar should minimize pruritus and scale. Intralesional corticosteroids may be used for persistent plaques. PUVA therapy (psoralen-UVA) and the systemic antimetabolite methotrexate are good therapeutic modalities in generalized severe cases.[4] However, the use of systemic drugs with or without adjuvant light in teenage psoriasis is limited to the most severe cases. Scalp disease is best treated with tar shampoos, corticosteroid solutions, and preparations of phenol and salicylic acid.

Lichen Planus

This is a disease of unknown etiology which affects skin and mucous membranes. The characteristic lesions are discrete, flat, polygonal, violaceous, shiny papules and plaques (Fig. 25-5). A scant scale may be presen. The lesions may koebnerize in sites of trauma and may be atrophic or verrucoid. Pruritus may be severe and keep the patient awake at night. Sites of predilection are flexor surfaces of the upper extremities, trunk, anterior lower extremities, inner thighs, genitalia, and buccal mucosa. Mucosal lesions characteristically have defined reticulated white streaks (Wickham's striae) and appear as white patches. The differential diagnosis includes papular secondary syphilis, psoriasis, and pityriasis rosea. Oral lesions can be mistaken for leukoplakia or aphthous ulcers. Intralesional triamcinolone (3–4 mg/ml) is most helpful.

Pityriasis Rosea

Pityriasis rosea is a noncontagious disease of unknown etiology which occurs primarily in young adults in late fall and spring. Spontaneous resolution occurs in 6–8 weeks. Recurrences are rare. The disease is characterized by discrete pinkish-red, oval, pruritic lesions with a fine scale which peels toward the margin (Fig. 25–6). A single large, oval patch may precede the rash by 2 to 10 days and is referred to as the "herald patch." The lesions are most commonly found on the chest and trunk and tend to parallel lines of clevage. The differential diagnosis includes tinea versicolor, macular syphilis, psoriasis, eczema, and seborrheic dermatitis. Therapy is required to relieve pruritus and includes emollient baths

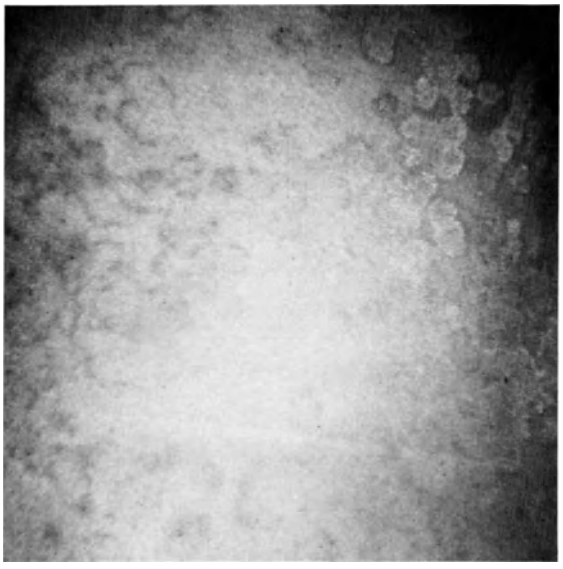

Figure 25-6. Pityriasis rosea.

and antihistamines. Areas exposed to sunlight or ultraviolet light clear more rapidly.[5]

Fungus Diseases

Fungi are microscopic members of the plant kingdom. They can be pathogenic or part of the normal skin flora. Fungal disease may be either superficial, in which the microorganisms live on the dead horny skin surface, or systemic. A KOH examination should be performed in all suspected fungal cases. If the test proves negative, one should then obtain a fungal culture. Wood's light examination may be helpful (Appendix 25–1).[6]

Dermatophytes

The dermatophytic infections are the superficial fungal infections which invade keratinized tissues such as the upper skin layers, hair, and nails. They are primarily caused by the genera *Epidermophyton, Microsporum*, and *Trichosporum*. Tinea refers to any superficial fungal skin infection. The word following tinea describes the location of the infection.

Tinea Capitis

This disease of childhood presents with annular patches of hair loss with varying degrees of inflammation. A tender mass called a kerion may develop with marked inflammation. Alopecia areata and self-induced hair loss (trichotillomania) must be ruled out. Griseofulvin, an antifungal antibiotic, cures tinea capitis in 6–8 weeks.

Tinea Corporis

Ringworm of the smooth skin is characterized by pruritic, red patches with central clearing and a scaly annular border (Fig. 25-7). Concentric rings can develop. The trunk and extremities are commonly involved; however, any part of the body can be affected. The differential diagnosis includes eczema, seborrheic dermatitis, and psoriasis. Topical antifungal treatment is usually curative in 4–6 weeks. Resistant or generalized cases should be treated with griseofulvin.

Tinea Cruris

This pruritic infection which occurs most commonly in men is known as "jock itch." It presents as uni- or bilateral reddish, scaly, well-demarcated lesions with raised borders. Sites of predilection are the groin, perineum, perianal region, and inner thighs. The differential diagnosis includes *Candida* infection, psoriasis, and erythrasma. Topical antifungals are usually sufficient to clear limited lesions. Extensive disease is best treated with griseofulvin.

Tinea Pedis

In athlete's foot, the primary eruption may begin as variously sized vesicles. Chronic scaling of the soles or a vesicular patch on the

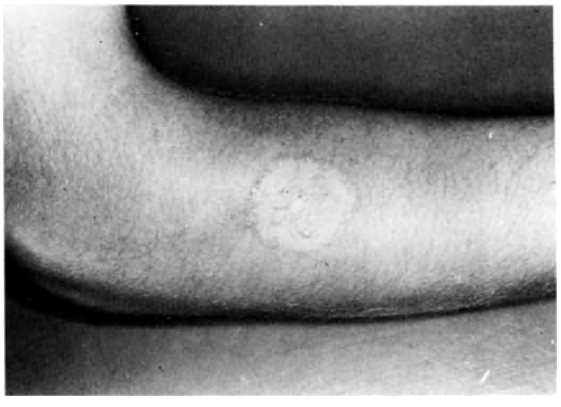

Figure 25-7. Tinea corporis.

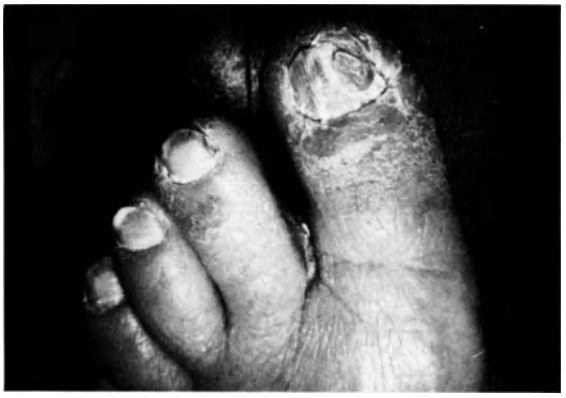

Figure 25-8. Onychomycosis.

dorsum of the foot can be present. Secondary pyogenic infection is not uncommon. The differential diagnosis includes contact dermatitis, psoriasis, and dyshidrosis. Good foot hygiene and a topical antifungal agent in early cases will achieve adequate control. With vesicular eruptions, wet compresses should be applied. Systemic antifungal and antibiotics are indicated for resistant or for superimposed bacterial infection.

Onychomycosis

This fungal infection involves invasion of the nail plate. Early yellow or white discoloration of the lateral border of the nail occurs. The brittle nail thickens and becomes distorted with subungual hyperkeratosis (Fig. 25-8). Lichen planus of the fingernails, as well as psoriasis, must be ruled out. Onychomycosis is very resistant to all forms of therapy. The best prognosis for cure is griseofulvin or Nizoral after surgical nail avulsion.

Yeasts

Yeasts are unicellular fungi that reproduce by budding.

Candidiasis (Moniliasis)

Candida albicans is a normal skin and gastrointestinal tract inhabitant. Moniliasis is primarily a cutaneous or mucocutaneous disease caused by *C. albicans*.

Intertrigo. Cutaneous moniliasis is more common in warm weather, diabetics and obese people, users of broad spectrum antibiotics, and in areas of moist macerated skin. The typical lesion is a bright-red, well-defined eroded area with satellite vesiculopustules. The areas primarily infected are the axillae, inframammary folds, groin, and toewebs (Fig 25-9). Topical antifungal agents and keeping the involved area dry are usually effective.

Paronychia. Paronychia is manifested by painful swelling and inflammation of the skin surrounding the involved nails. Pus can sometimes be exposed and then cultured. Dystrophic nail changes can occur. It is common in individuals who frequently immerse their hands in water. One must rule out a bacterial infection. Topical antifungal agents and avoidance of excessive water are necessary.

Generalized Moniliasis. This rare infection is seen in debilitated patients and is very resistant to therapy. Septicemia can occur. Treatment with oral Nizoral may be indicated.

Thrush. Thrush is characterized by creamy, white patches on an inflamed mucous membrane. It can involve the oral mucosa and tongue. It is seen commonly in infants and debilitated or immunosuppressed patients. Treatment with 1% gentian violet or antimonilial lozenges is effective.

Vulvovaginitis. An inflamed vaginal mucosa surrounded by erythemaous skin and containing a thick cream-white discharge is characteristic of moniliasis. It is common in diabetics and pregnancy. Trichomonal vag-

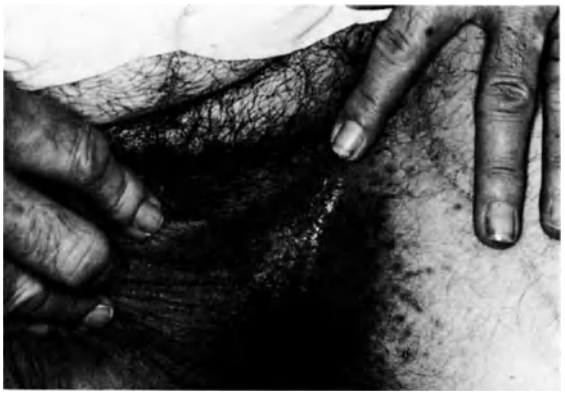

Figure 25-9. Intertrigo.

initis must be ruled out by culture or KOH. Vaginal antifungal suppositories and topical creams are indicated.

Tinea Versicolor

Tinea versicolor is a chronic, somewhat pruritic, superficial fungal infection caused by *Malassezia furfur*. This organism represents the pathogenic form of the yeast, *Pityrosporon orbiculare*, a normal skin inhabitant. Slightly scaly, hypo- or hyperpigmented patches which appear lighter in winter and do not tan in the summer are characteristic. It is more prevalent in the summer and tends to recur. It primarily occurs on the upper chest, back, neck and arms. Differential diagnoses includes vitiligo and pityriasis rosea. The short hyphae and spores on KOH examination appear as "spaghetti and meatballs." It cannot be cultured. Treatment with selsun lotions or shampoos for several weeks is necessary. Adjuvant topical antifungal creams can be of benefit.

Bacterial Infections

The skin contains normal nonpathogenic bacteria in large populations. These include *Corynebacterium, Staphylococcus epidermidis*, and some gram-negative organisms. However, immunosuppression, trauma, diabetes mellitus, corticosteroids, and immunodeficient states can give any bacteria the opportunity to cause disease. Infectivity is determined by the organism's pathogenicity, site of entry, and the host's defense toward it.

Impetigo

This superficial infection occurs at any age but is more infectious in infants and young children. It may be a secondary complication of any eczematous lesion. Initially, pruritic vesicles appear and then rupture, exuding a purulent exudate which forms honey-colored crusts. It is generally caused by coagulase-positive staphylococci and occasionally streptococci. If Group A beta-hemolytic streptococci are cultured, the patient should be observed for the development of acute glomerulonephritis. Impetigo is seen most often on the face and extremities. Bullous lesions caused by *S. aureus* Group II occur particularly in nasal carriers. Herpes, tinea, and contact dermatitis are included in the differential diagnosis. Depending on the culture results of the vesicular fluid and/or crusts, penicillin, erythromycin, or the appropriate broad spectrum antibiotic should be administered. Removal of the crusts with warm compresses is effective. The use of adjuvant topical antibiotics is debatable.[7]

Folliculitis

Folliculitis is an infection within hair follicles. It is often related to poor hygiene, friction, or chemical exposure. The lesions are usually multiple papules or pustules caused by coagulase-positive staphylococci. The areas most commonly involved are extensor surfaces of the extremities, buttocks, face, and scalp (Fig. 25–10). Local treatment with warm compresses and, if necessary, broad spectrum antibiotics are very helpful. The differential diagnosis includes milia and acne.

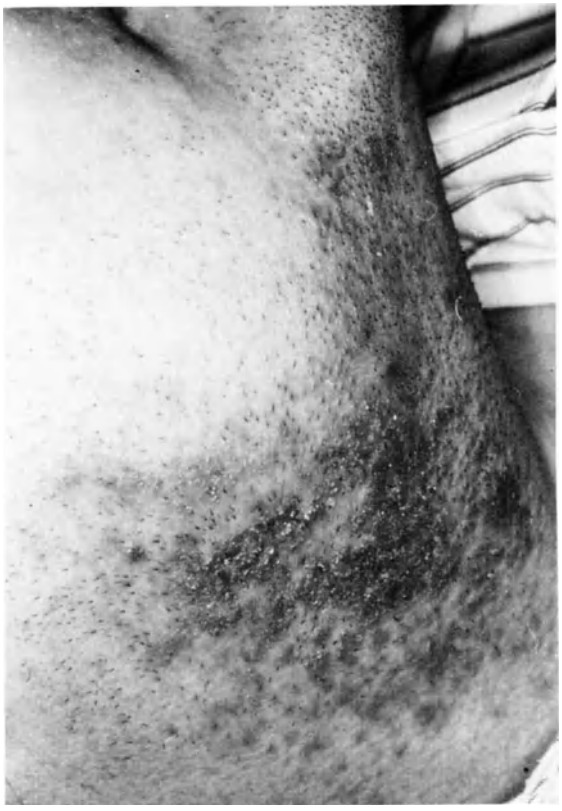

Figure 25-10. Folliculitis.

Furuncles and Carbuncles

Furuncles and carbuncles are more extensive infections of the hair follicle. A furuncle is a deep-seated inflammation of a hair follicle unit. Carbuncles involve several follicles and may drain to the surface through several points. Carbuncles are generally larger and deeper. They both appear as red, hot, tender nodules often with a central pustular area (Fig. 25-11). Sites of predilection are the beard, axilla, groin, and buttocks. The differential diagnosis includes cystic acne and hidradenitis suppurativa. Pending culture results, use of an antibacterial soap and prompt systemic antibiotic therapy are indicated. Large lesions may require incision and drainage.

Cellulitis and Erysipelas

Cellulitis is a subcutaneous tissue infection caused by Group A beta-hemolytic streptococci. The area has poorly defined borders, and is erythematous, hot, and tender with red streaks extending proximally from the lymphatics. It is often preceded by trauma.

Erysipelas is a superficial cellulitis with marked erythema and well-defined borders. It occurs most commonly on the face or legs (Fig. 25–12). Both may have systemic signs of infection, lymphadenopathy, and fever. The differential diagnosis includes acute contact dermatitis, herpes zoster, and thrombophlebitis. Penicillin or erythromycin are the drugs of choice. A patient with constitutional symptoms or extensive disease may require hospitalization.

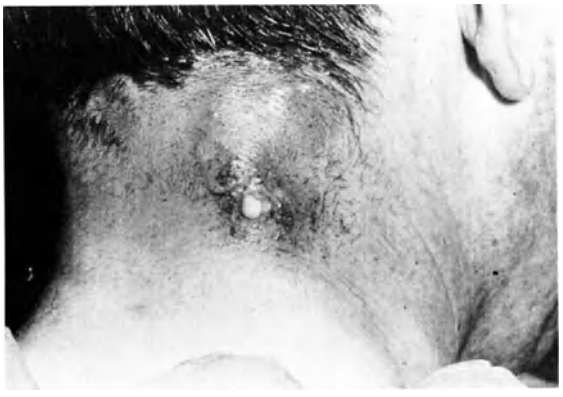

Figure 25-11. Furuncle.

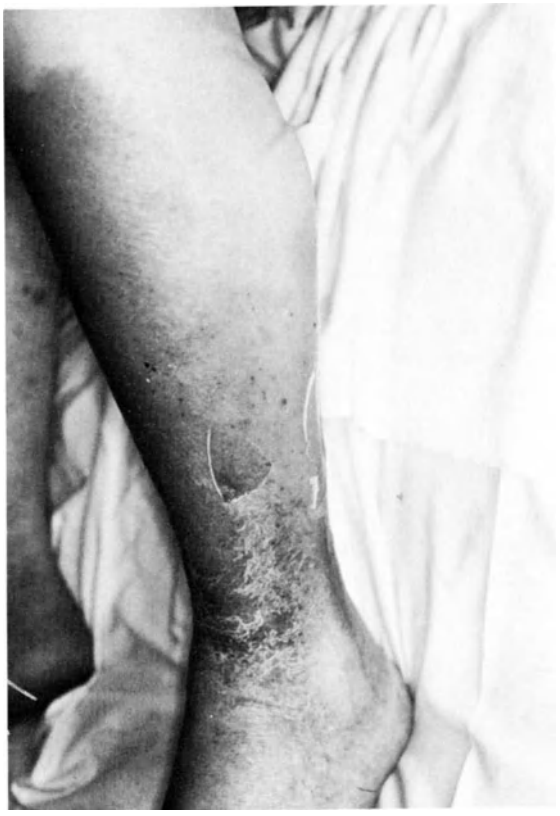

Figure 25-12. Erysipelas.

Erythrasma

Erythrasma is a superficial bacterial infection caused by *Corynebacterium minutissimum*. It presents as a pruritic, brownish-red, scaly, sharply marginated plaque in the intertriginous areas or the toe web spaces. It is more common in obese and diabetic patients. The differential diagnosis includes moniliasis, superficial fungal infections, and dermatitis. Bacterial cultures are negative. These lesions fluoresce coral-red under Wood's light (Fig. 25-13). Systemic erythromycin or topical antibacterial soaps are usually curative. Recurrences are common.

Parasites and Insects Infestations

Scabies

Scabies is a contagious disease caused by the mite *Sarcoptes scabiei*. Initial lesions are papules and vesicles are extremely pruritic at night.

Figure 25-13. Erythrasma.

Pathognomonic is the "burrow," an erythematous threadlike line composed of eggs and fecal material. It most commonly occurs in the webs of fingers, flexor surfaces of the wrists and forearms, elbows, axillae, breasts, abdomen, genitalia, and buttocks (Fig. 25-14). The differential diagnosis includes bug bites, neurotic excoriations, and pediculosis. Scraping a burrow with a scalpel blade covered with mineral oil or KOH and then observing the material by microscopic examination should yield positive results. Specific therapy is the application of gamma benzene hexachloride (Kwell) lotion to the entire body. Prophylactic treatment of other family members is advocated. Directions must be explicit and no refills are given on the prescription. Cases of CNS toxicity have been reported in small infants from misuse. If pruritus persists for 3 weeks, reexamine the patient.

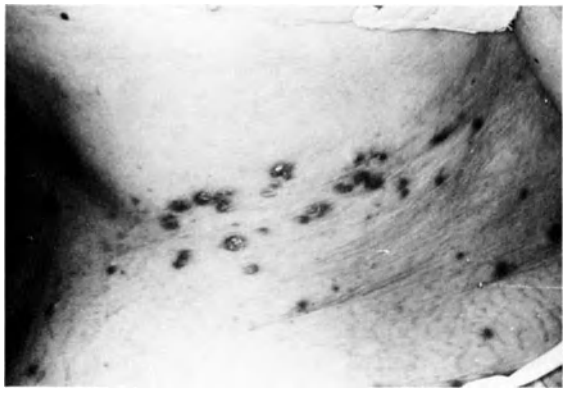

Figure 25-14. Scabies.

Pediculosis

Lice infects all ages and occurs most commonly in those of lower income because of lack of cleanliness. Three clinical entities are produced: (1) head lice, *Pediculosis capitis*; (2) body lice, *P. corporis*; and (3) pubic lice, *P. pubis*. The lice bite the skin and live on blood meals. Erythematous, excoriated, pruritic papules may be present. Bluish-gray patches (maculae caeruleae) may occur in the pubic area. Visible eggs or nits are attached to hairs or clothing. The differential diagnosis includes flea bites and scabies. Treatment includes the following:

1. Head lice: apply gamma benzene hexachloride (Kwell) shampoo for 4 minutes and then shampoo and repeat in 7 days. Tweezers or a comb dipped in vinegar will facilitate removal of nits. Examine all contacts.
2. Body lice: apply Kwell lotion from neck downward and leave on overnight. Launder in boiling water or dry clean all clothing.
3. Pubic lice: treat as for body lice. Check all sexual partners. Pubic lice can occur in eyelashes and blepharitis may result. If this occurs, petrolatum should be applied twice daily to the eyelashes for 10 days.[8]

Spider Bites

Brown Recluse

Loxosceles reclusa is a 1-cm dark brown spider with a violin-shaped marking on the cephalothorax. Most cases have been found in the central United States. Within the first 8 hours after the bite, a tender bulla with surrounding erythema develops. Subsequent ulceration and even gangrene may develop within a week. Treatment should be individualized as spontaneous regression may occur. Systemic or intralesional corticoseroids, dapsone,[9] and surgical excision have been used.

Black Widow

Lactrodectus mactans is a 12-mm black spider with a red hourglass on its abdomen. It occurs anywhere in the United States. The bite is usually inconspicuous and occurs on the

genitals or buttocks. Within minutes severe pain, nausea, myalgia, and even convulsions may occur. Antivenin (Merck Sharp & Dohme) is recommended if given early. Systemic corticosteroids and/or calcium gluconate are beneficial in relieving muscle spasms. Morphine may be necessary for pain and sedation.

Chiggers

Chigger bites are pruritic urticarial papules caused by the mite *Trobicula alfreddugesi*. They occur on the flexural wrist surface, belt line, brassiere line, or neckband area. Excoriation can lead to secondary infection. Treatment is mainly symptomatic and includes oral antihistamines and intralesional triamcinolone (3 mg/ml) for severe cases.

Fleas

Flea bites are one of the more common causes of papular urticaria in children and adolescents. The lesions are small vesicles or papules which occur about the legs and waist.

Tick Bites

Ticks are bloodsucking arachnids, larger than mites. Their bites may produce pruritic papules and even nodules. *Dermacentor andersoni* and *D. variabilis* are vectors of Rocky Mountain spotted fever, which is more common in the southeastern United States. The incubation period is 5–10 days. Initial symptoms are myalgia, headache, and fever. Three to 5 days later a maculopapular rash appears on the distal extremities and spreads proximally. Complement fixation titers and cutaneous biopsy for immunofluorescence should be obtained. Intravenous tetracycline or chloramphenicol is the treatment of choice. The differential diagnosis includes meningococcemia and gonococcemia.[10]

Allergic Reactions

Allergy is an acquired alteration in the ability of an organism to react. The delayed type of hypersensitivity due to sensitized T-cells is seen in contact dermatitis to plants, topical medications such as neomycin, and metals (nickel and chromium). After initial exposure, a period of 10–14 days must elapse during which time hypersensitivity develops. Upon reexposure (as with tuberculin injection) a reaction will develop within 48 hours. Poison ivy dermatitis presents as a linear vesicular eruption in the areas exposed to the antigen. A pruritic papulovesicular rash may develop in the perineum after repeated exposure to neomycin, or a similar eruption may develop on the thighs after exposure to undergarments containing metal clasps.

Urticaria (Hives)

Urticaria is characterized by the appearance of pruritic, erythematous, slightly raised irregular lesions which blanch with pressure, indicating the presence of dilated blood vessels and edema (Fig. 25-15). This reaction is

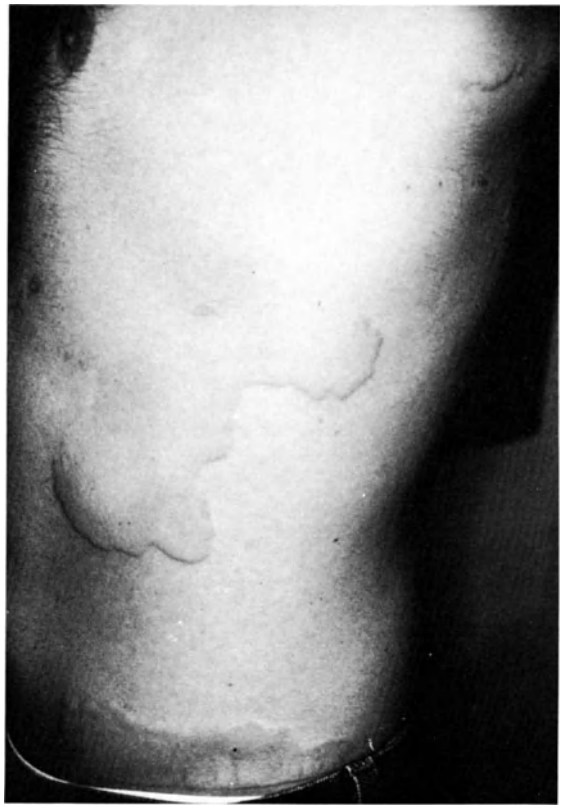

Figure 25-15. Urticaria (hives).

primarily due to the release of histamine from the mast cells. Most cases of hives are due to hypersensitivity to drugs, viral or bacterial agents, food allergies, or psychogenic factors. Heat and pressure may also induce urtication. Aspirin and codeine are primary histamine releasers and therefore should be avoided since they produce hives in individuals with a propensity to urticate.

When urticaria persists for several weeks, a more intensive investigation is necessary. Chronic urticaria may be due to localized or systemic infections, malignancies, or collagen vascular diseases. In such individuals, CBC, sedimentation rate, urinalysis, ANA, stools for ova and parasites, and chest radiography may be indicated. Urticaria is best treated by using three antihistamines at one time, each in moderate doses. An elimination diet to avoid aspirin, codeine, sea food, strawberries, pork, citrus, cheese, and nuts is advisable.[11]

Photosensitivity Dermatoses

A number of substances known as photosensitizers may induce an abnormal response when the skin is exposed to sunlight. Photosensitivity may be divided into phototoxic and photoallergic reactions. A phototoxic reaction is an exaggerated sunburn-type reaction. It develops initially in most persons exposed to the photosensitizing substance when the skin is exposed to light of the proper wavelength. This is seen with certain antibiotics such as tetracycline or declomycin and with the psoralen group of compounds.

A photoallergic reaction is an unusual allergy which first requires a primary exposure to the substance so that an altered state of reactivity may develop. The clinical response to photoallergic reactions differs from the sunburn response seen with phototoxic reactions in that after exposure to light, a papulovesicular or exudative plaque–type response may develop. This need not remain localized to light-exposed areas as with phototoxic reactions, but may become generalized. This type of reaction is seen with thiazides, phenothiazines, sulfonamides, and sulfonylurea hypoglycemics. Porphyrin studies should be obtained when the cause of the photosensitivity is not apparent.

Glandular Disorders

Sebaceous Glands

Acne

Acne Vulgaris. Acne vulgaris is the most common cutaneous disorder in adolescents. The basic cause is unknown. However, *Corynebacterium acnes* plays an important role in acne pathogenesis. The disorder may be associated with an endocrine imbalance, heredity, diet, cleanliness, general health, and emotions. Patients often have an oily complexion and scalp. The primary lesions are open comedones (blackheads) and closed comedones (whiteheads). Papules, pustules, and cysts can also be present. Secondary lesions are scars, pits, and excoriations (Fig. 25-16).

The severity of acne is classified as grade I, comedones; grade II, comedones and pustules; grade III, comedones, papules, pustules, and scars; and grade IV, grade III plus cystic lesions, sinus tracts, and numerous scars.

The clinical course includes exacerbations and remissions. Cutaneous regions with abundant sebaceous glands such as the face, back, and chest are the sites of predilection. The differential diagnosis includes halogene acne, impetigo, and folliculitis. Treatment must be individualized for each patient. Tetracycline is the initial systemic drug of choice. For grades II–IV response is noted in 2–4 weeks. Alternate antibiotics are Minocin, erythromycin, and Bactrim. Side effects of

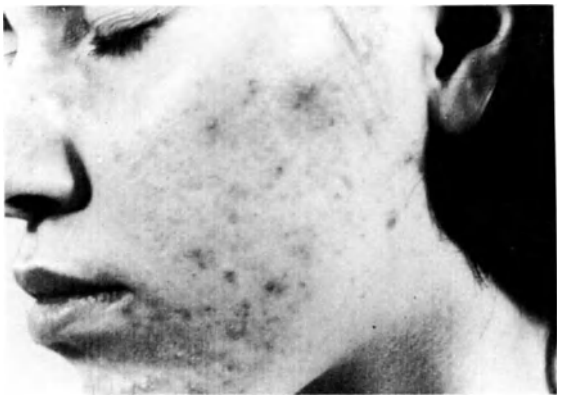

Figure 25-16. Acne vulgaris.

tetracyclines are vaginal moniliasis and gastric upset. Tetracycline should not be used in anyone under 12 years of age as it will permanently stain developing teeth. Topical antibiotics such as clindamycin and erythromycin in 1–2% concentration may be used in younger patients, mild acne, or in conjunction with systemic antibiotics.

Comedolytic agents such as tretinoin (Retin-A) or benzoyl peroxide are highly effective with/without antibiotic therapy. They can be used at any age. Irritant side effects are common; therefore therapy should begin with weaker preparations.

Systemic corticosteroids can be useful in short-term therapy for severe inflammatory cases. Their use in acne therapy should be reserved. Intralesional triamcinolone (3 mg/ml) with a 30-gauge needle heals large pustules and cysts in 2 to 3 days. Topical hydrocortisone preparations used sparingly can decrease inflammation.[12]

Oral contraceptives may have a profound effect on premenstrual exacerbation of acne. Pills high in estrogen often improve acne. Oral dexamethasone in low doses has proven to have similar effects. Cleansing should be done with a mild soap such as Dove, Neutrogena, or Basis Soap. Soaps containing benzoyl peroxide derivatives have a drying effect. It is necessary to avoid excessive scrubbing and devices which can irritate the skin.[13]

The synthetic retinoids are a new class of drugs which are highly effective in treating severe cystic acne. Accutane (13-*cis*-retinoic acid) is the first such compound approved in the United States. Patients should be 12 years of age or older as Accutane treatment during childhood may result in bone toxicity. Bone changes such as cortical hyperostosis and periosteal hyperreactivity have been seen. Sexually active females should use some means of contraception as there is a significant risk of teratogenicity. Dosage at 0.5–2.0 mg/kg/day for 4–6 months is indicated for severe cystic acne. Because of the continued healing, 2-month treatment-free evaluation periods are useful in patients requiring additional therapy. Blood work is necessary before and during therapy. Major symptoms of toxicity are mucocutaneous drying, musculoskeletal pains, and transient triglyceride and transaminase elevations. These are all dose related.[14]

Acne surgery including comedone expression and draining of cysts helps to reduce the size and severity of scarring. Exposure to sunlight or UVB sunlamps is very effective in some patients.

Steroid Acne. This is a secondary type of acne produced by hyperfunction of the adrenal cortex or from the administration of systemic steroids. It is characterized by extensive papulopustular lesions without comedones. Treatment involves eliminating the source of excessive steroids.

Acne Conglobata. This severe form of acne occurs primarily in males. It involves the entire back, and sometimes the buttocks and anogenital area. Acne conglobata has numerous groups of giant comedones, subcutaneous necroses, ulcerations, and fistulous tracts (Fig. 25-17). Healing occurs by atrophic or hypertrophic scarring. Systemic antibiotics, intra-

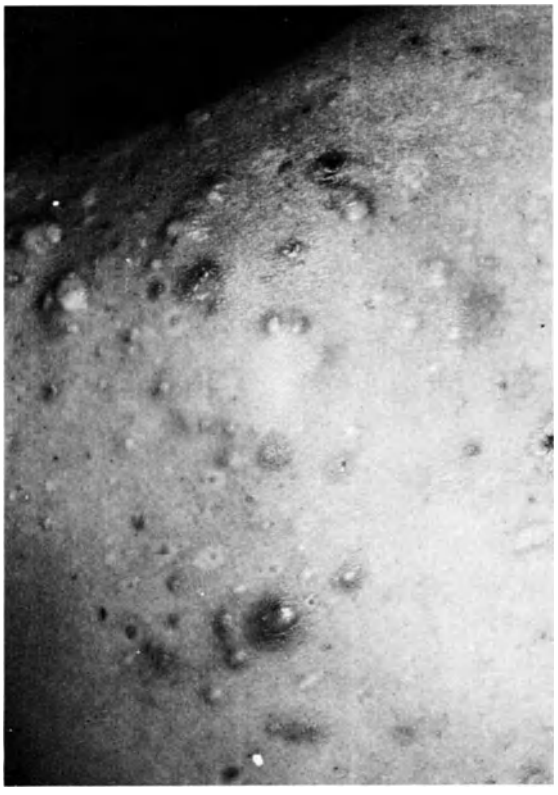

Figure 25-17. Acne conglobata.

lesional corticosteroids, and synthetic retinoids can be effective.[15]

Milia

Milia are asymptomatic smooth, white, tiny cystic lesions filled with cheesy material. The site of predilection is the face, especially around the eyes. The etiology is unknown; however, some develop after trauma to the skin. They must be differentiated from comedones. Removal by a comedo extractor or puncturing the lesion with a sharp-pointed blade and expressing the contents is usually successful.

Nevus Sebaceous of Jadassohn

Nevus sebaceous is a circumscribed yellow-brown plaque with either a smooth or verrucoid surface (Fig. 25-18). They are congenital lesions primarily located on the scalp. Complete excision is indicated as 10% of patients develop a basal cell carcinoma or may contain other hamartomas. The differential diagnosis includes other types of nevi and viral warts.[16]

Apocrine Glands

Fox-Fordyce Disease

Fox-Fordyce disease is a rare, intensely pruritic, chronic papular dermatosis of the axillae and pubic area (Fig. 25-19). It occurs most commonly in adolescent females. The hair in these areas is scanty. The etiology is presumed to be an endocrine imbalance. The treatment centers around estrogens, primarily oral contraceptive pills. The differential diagnosis includes an irritant folliculitis.

Figure 25-18. Nevus sebaceous of Jadassohn.

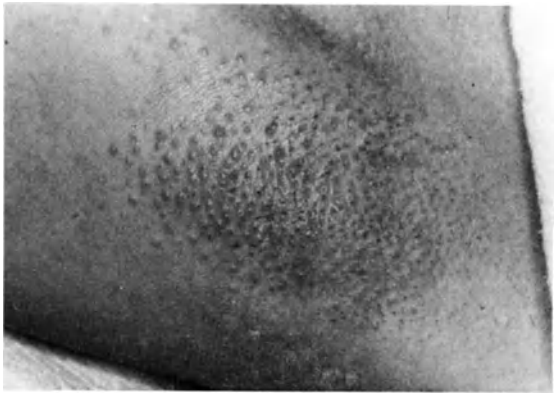

Figure 25-19. Fox-Fordyce disease.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic, recurring, pyogenic, and scarring disease of the apocrine glands primarily located in the axilla, mammary, genitocrural, and perianal regions. It does not occur before puberty and is often associated with cystic acne. The cause is unknown but hormones, obesity, and follicular plugging are contributory. Complications include anemia and squamous cell carcinoma. Bacteriologic culture with sensitivity from the lesions should be obtained. Treatment includes oral antibiotics, incision and drainage of larger lesions, intralesional triamcinolone (10 mg/ml), germicidal soap, and if the response is not satisfactory surgical excision may be necessary.[17]

Eccrine Glands

Hyperhidrosis

Hyperhidrosis is an excessive increase in perspiration. It is aggravated by stress and is frequently seen in adolescents. The axillae, palms, soles, and face are frequently affected. Generalized hyperhidrosis may be associated with endocrine abnormalities, drugs, or nervous system disorders. Drysol (topical aluminum chloride solutions) may provide temporary relief.

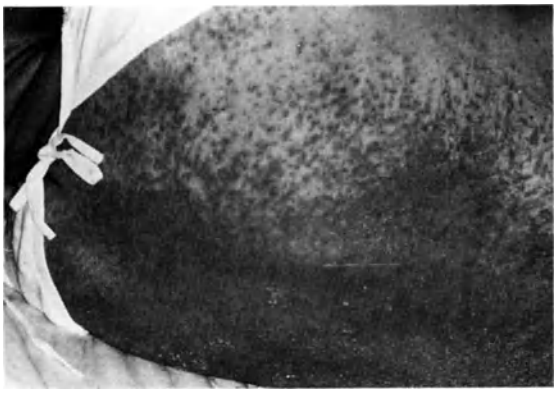

Figure 25-20. Miliaria.

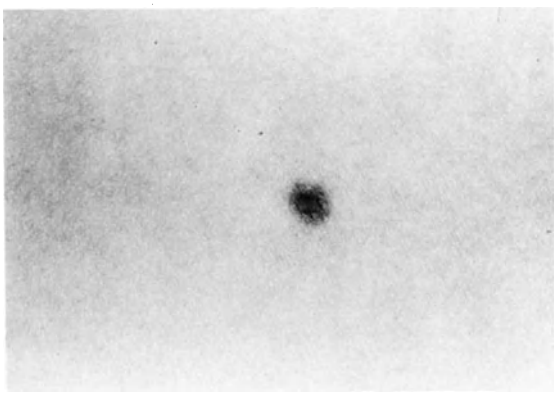

Figure 25-21. Junctional nevi.

Miliaria

"Prickly heat" is an acute pruritic papular rash with tiny clear vesicles or pustules caused by occlusion of the sweat ducts. It is associated with excessive perspiration and hot weather, and appears mainly on the trunk, neck, and intertriginous areas, as well as sites of clothing friction (Fig. 25-20). The differential diagnosis includes folliculitis, acne vulgaris, and atopic dermatitis. The most effective treatment is to place the patient in a cool environment and avoid excessive perspiration. Colloidal oatmeal baths and antihistamines can be beneficial. It is necessary to do a KOM prep as *Candida* can be a secondary invader.[18]

Neoplasms

Benign Neoplasms

Nevi

Nevi (moles) are tumors of the skin that contain nevus cells and are multiple in type. The incidence of nevocellular nevi rises sharply in adolescence. The tendency to have large numbers is familial and a sudden increase may occur in pregnancy. Diagnosis and classification is histologic rather than clinical.

Junctional Nevi. These lesions are generally flat, smooth, hairless, tan or dark brown, 1 mm to 1 cm in size, well-defined and bordered lesions (Fig. 25-21). Childhood nevi are mainly junctional.

Dermal Nevi. These are mature lesions which may be pigmented or nonpigmented. They are often dome-shaped, hairy, and virtually always benign.

Compound Nevi. These are combinations of junctional and intradermal nevi. They generally are raised or papillomatous, light brown, and round or oval.

Spindle Cell Nevus (Spitz Nevus). Benign juvenile melanoma is a smooth, dome-shaped, hairless, purplish-red nodule which generally occurs on the face of children or adolescents. Despite their histologic characteristics of melanoma, they do not behave like malignant lesions. Conservative surgical excision is advised.

Blue Nevus. This benign pigmented nodule possesses a blue color and usually occurs as a solitary lesion on the dorsal surface of the hands, face, or buttocks.

Halo Nevi. These are dark nevi, usually on the trunk, surrounded by an area of white depigmentation (Fig. 25-22). They are thought to be a result of an immune reaction in which the nevus cells are destroyed by lymphocytes.

Ephelis. A freckle is a transient increase of epidermal pigment without an increase in nevus cells.

Congenital Nevocellular Nevi. These distinctive nevi are present at birth and tend to follow a

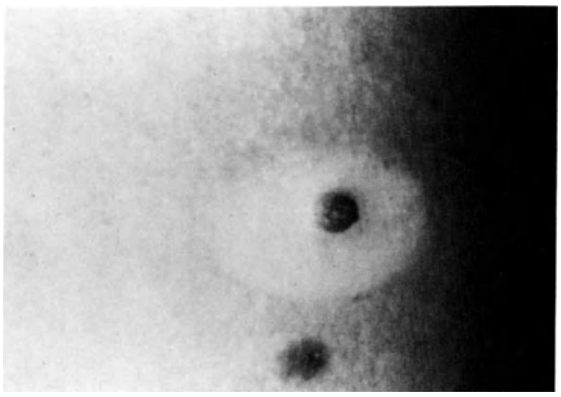

Figure 25-22. Halo nevus.

dermatomal pattern. The incidence is less than one per 1000 births. They are usually brown with coarse hairs on the surface. The surface is nodular, papillated, or verrucoid with well-defined borders. The lesions darken, thicken, and become more hairy with time. On the trunk, larger lesions are referred to as "bathing trunk nevi" (Fig. 25-23). Nevi on the scalp may involve the underlying meninges. These nevi have a significant predisposition to malignant melanoma. Studies suggest that melanoma develops in 2–31% of congenital nevocellular nevi, with the malignant change occurring most frequently in childhood and adolescence. Therefore, 1.1% of malignant melanomas occur in congenital nevi. It is best to excise the lesion and follow with skin grafting when necessary. Dermabrasion in early infancy of very large lesions is debatable. The risk of death from general anesthesia is substantially less than the risk of malignant degeneration.

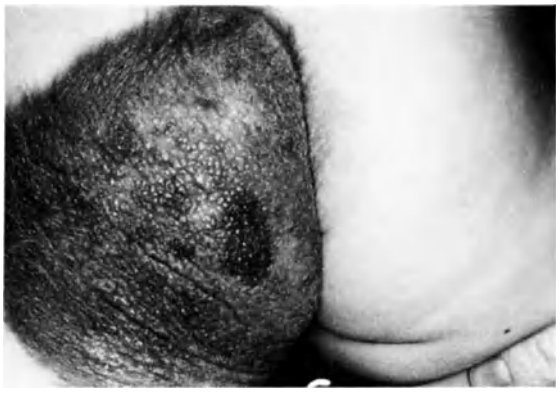

Figure 25-23. Congenital nevocellular nevi.

Danger signals in any nevus are hemorrhage, itching, ulceration, rapid growth, inflammation, satellite lesions, and darkening. Some advocate removing nevi on the palms, soles, or genitalia. Removal by shaving, punch biopsy, or excision can be performed. All specimens should be sent for histologic examination.[19]

Hemangioma

Hemangiomas are congenital vascular abnormalities of the skin. Heredity does not play a factor. There are several types which vary as to depth, clinical appearance, and location.

Superficial Hemangioma. Capillary hemangiomas (port-wine stains) are raised, red to bluish-red, soft lesions generally found on the face, neck, or shoulders. Spontaneous resolution is usual.

Cavernous Hemangioma. These hemangiomas are soft, rounded, red-purple tumors which are often associated with a capillary hemangioma and involve larger vessels (Fig. 25-24). Generally, they present their full extent at birth and show less tendency to involute. Extensive lesions may be associated with the development of thrombocytopenic purpura (Kasabach-Merritt syndrome). Treatment is indicated in rapidly growing lesions or lesions which compress a body orifice. A short course of oral steroids or surgical or radiation therapy has proven successful.

Spider Hemangioma. Nevus araneosus is a small vascular lesion with a central red arteriole with radiating arms. Normally they are found on the face and upper chest. They are more common in pregnancy. Cosmetic treatment is obtained by using an epilation needle.

Pyogenic Granulomas. These vascular lesions occur frequently at sites of injury. They may become crusted and, if irritated, bleed profusely. They usually involve the face and extremities. The differential diagnosis includes verrucae, nevus, and foreign body granuloma. Diagnosis can be proven by biopsy. Removal is accomplished by excision or destruction of the lesion by electrodesiccation.

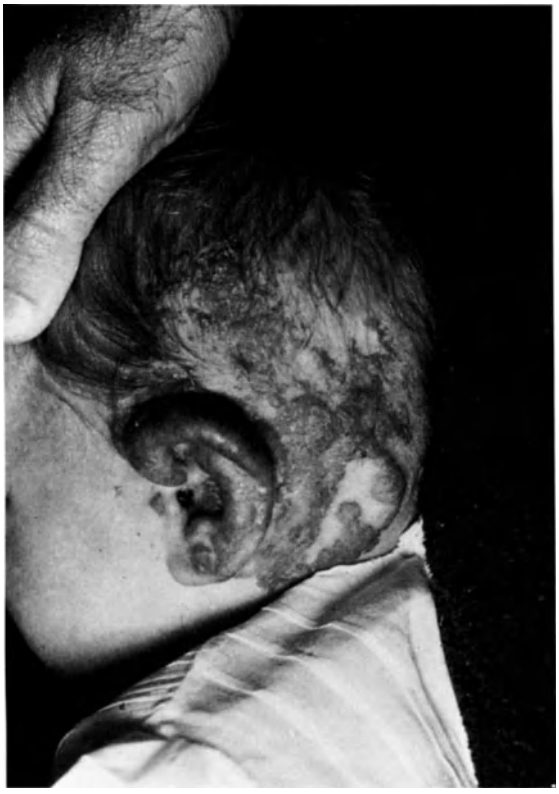

Figure 25-24. Cavernous hemangioma.

Dermatofibroma

These single, firm, dull red to brown nodules, less than 1 cm in size, are more common in women on the distal portions of the extremities. The differential diagnosis includes keloids or nevi. No treatment is indicated.[20]

Keloid

Keloids are firm, elevated, whitish-red, elastic nodules of scar tissue. Their surface is smooth and hairless. They tend to develop at sites of trauma. Keloids are most common in blacks and tend to be familial in Caucasians when they occur. The midsternal and back areas are the most common sites (Fig. 25-25). The differential diagnosis includes sarcoid and hypertrophic scar. Smaller keloids respond to intralesional triamcinolone (10 mg/ml). Larger keloids are excised, and this is followed by intralesional triamcinolone.[21]

Epidermoid and Pilar Cysts

These lesions are benign, elevated, firm, cystic growths attached to normal skin, often with a central pore. They are filled with a caseous, foul-smelling material. They may be solitary or multiple and are often associated with acne. The scalp, face, back, and scrotum are most commonly involved (Fig. 25-26). The differential diagnosis includes lipoma or a fibroma. Surgical excision is the preferred treatment.

Pilar cysts cannot be clinically distinguished from epidermoid cysts. They are usually on the scalp. The histologic pattern is distinct.

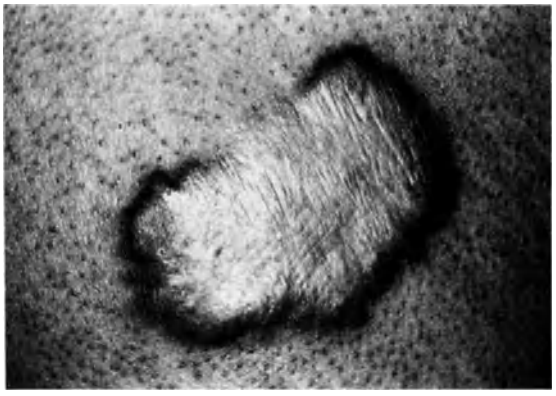

Figure 25-25. Keloid.

Lipoma

These subcutaneous fatty tumors are soft and covered with normal skin. There is a tendency for familial occurrence. They can occur anywhere on the body and may be multiple (Fig. 25-27). The differential diagnosis includes subcutaneous fibroma and epidermoid cysts. Excision is the therapy of choice.

Figure 25-26. Epidermoid cyst.

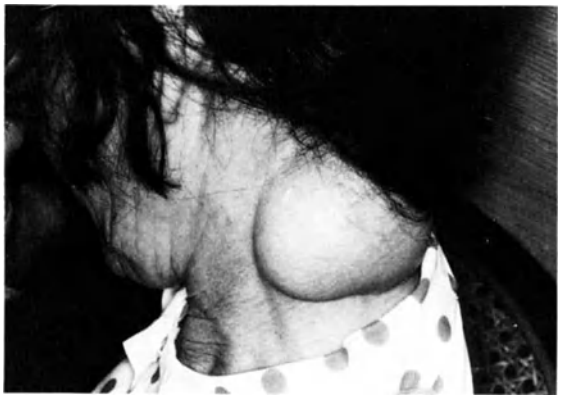

Figure 25-27. Lipoma.

Syringoma

These small, flat, skin-colored papules usually appear during adolescence as multiple lesions around the face, especially the eyelids. In addition, the neck, upper chest, and vulvar area are commonly involved. Syringomas must be differentiated from flat warts. Removal is for cosmetic purposes only.

Molluscum Contagiosum

This is a benign, mildly contagious, cutaneous tumor caused by the pox virus which spreads by autoinoculation. The lesions are asymptomatic, globular, umbilicated, skin-colored, waxy papules (Fig. 25-28). Sites of predilection for these multiple tumors are the face, extremities, trunk, and genitalia. Microscopic examination of the biopsy specimen, obtained by scraping the lesions with a curette or needle, reveals large intracytoplasmic inclusion bodies in the epithelial cells. The differential diagnosis includes milia and warts. Destruction of the lesions by curettage, liquid nitrogen, or electrofulgeration is curative.

Warts

Warts are autoinoculable cutaneous tumors induced by papovaviruses; immunosuppression enhances their proliferation. Some warts may regress spontaneously, whereas others are extremely refractory to treatment. Children and adolescents are frequently affected.[22]

Verruca Vulgaris. The common wart is a dome-shaped, cauliflower-surfaced, firm nodule seen primarily on the hands, knees, and elbows. Filiform or threadlike warts are pedunculated and generally occur on the face and neck (Fig. 25-29). Periungual warts are not uncommon. The differential diagnosis includes molluscum contagiosum and seborrheic keratosis. Cryosurgery or curettage and electrodesiccation are most effective.

Verruca Plantaris. Plantar warts are usually multiple, painful, hyperpigmented lesions generally located over pressure points on the soles. They are often mistaken for callus. However, paring their surface reveals black pinpoint areas. Treatment involves paring the lesion, followed by cryosurgery, application of a keratolytic solution, and placement of a 40% salicylic acid plaster.

Verruca Planae. These lesions are multiple, flat-topped, hyperpigmented papules generally seen on the face and dorsum of the hands. They can easily be mistaken for molluscum.

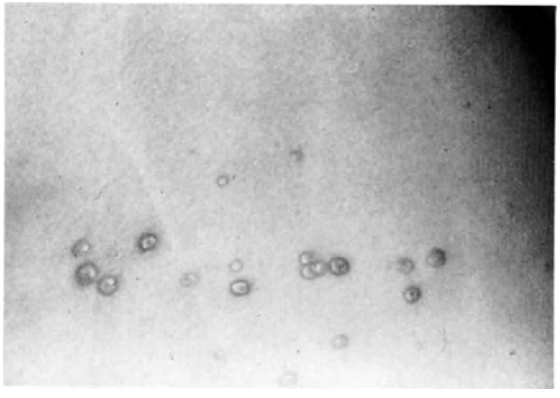

Figure 25-28. Molluscum contagiosum.

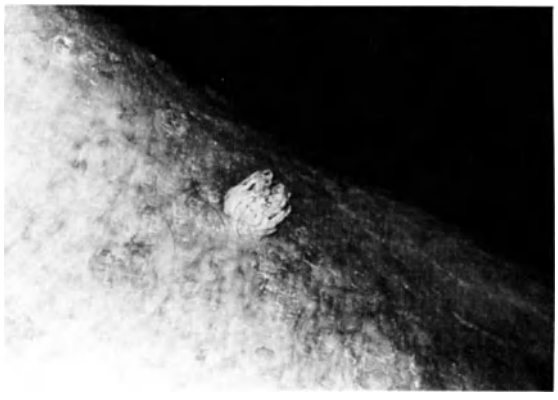

Figure 25-29. Verruca vulgaris.

Flat warts are resistant to most therapy but superficial desiccation and curettage or light freezing may be of value.

Verruca Acuminata (Venereal Warts). These appear initially as a small pointed projection in the anogenital area. They may multiply to form large vegetating masses. Such warts usually respond to painting with podophyllin.

Acrochordons (Benign Papilloma)

Skin tags are small, flesh-colored or dark brown papules or filiform tags. They are seen most commonly on the neck, upper chest wall, and axillae. The differential diagnosis includes nevi or filliform verrucae. Therapy consists of scissor excision or desiccation.

Malignant Neoplasms

Malignant Melanoma

A neoplastic melanocyte disorder, this is the most malignant primary cutaneous disorder. Malignant melanomas are classified as (1) lentigo maligna, (2) superficial spreading melanoma, and (3) nodular melanoma. Melanomas most commonly affect patients with fair skin, blue eyes, and red or blond hair. Reports of familial cases have been documented. Approximately 65% of these lesions arise in a preexisting nevus. Some malignant melanomas (1.1%) occur in congenital nevi. Most melanomas are smooth, nonhairy, colorless to black lesions, with irregular or speckled pigment and ill-defined borders (Fig. 25-30). Bleeding, ulceration, nodule formation, color change, and evidence of metastases may occur. Any area of the body may become involved. The differential diagnosis includes pigmented moles, pigmented seborrheic keratosis, and pyogenic granulomas. Treatment is based on the depth of invasion of the tumor and the presence or absence of metastasis.[23]

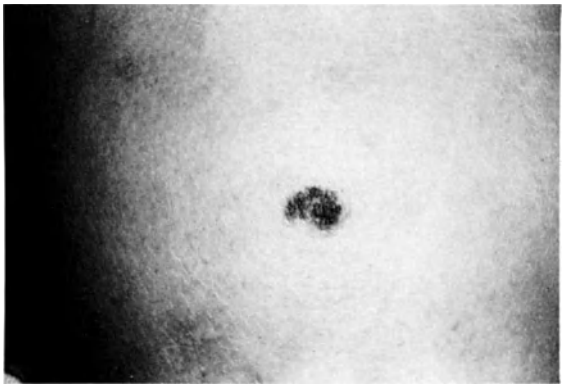

Figure 25-30. Malignant melanoma.

Miscellaneous Neoplasms

Lichen Sclerosus et Atrophicus

Lichen sclerosus et atrophicus is a dermal connective tissue disease of unknown etiology. It is seen more commonly in the preadolescent period and in females. This chronic condition is characterized by pinkish-white papules that coalesce into plaques. With time, atrophy and keratinous plug information (delling) occur. In females, most are vulvar and perineal lesions with an hourglass pattern, associated pruritus, and discharge (Fig. 25-31). In males, the disorder is called balanitis xerotica obliterans. Extragenital involvement is not un-

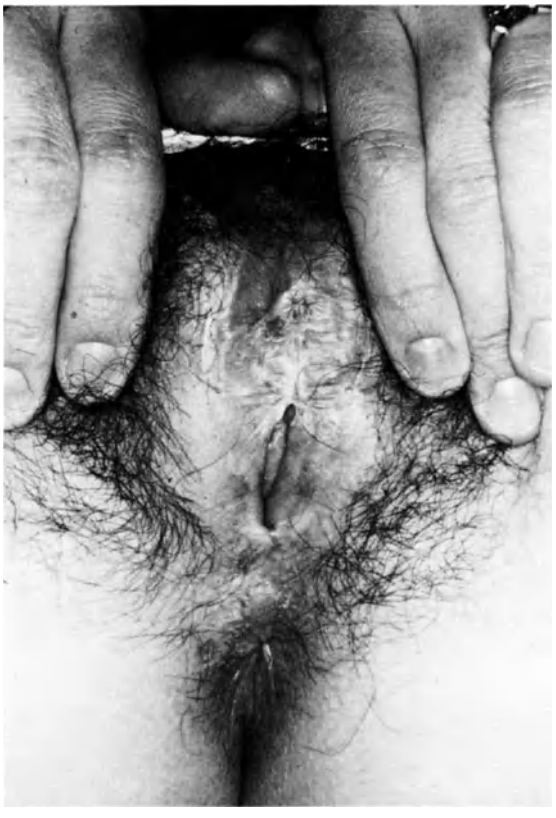

Figure 25-31. Lichen sclerosus et atrophicus.

common. The differential diagnosis includes vitiligo, morphea, and lichen planus. Two-thirds of childhood lesions undergo involution by the time of puberty without atrophy. The condition persists in the remaining one-third with atrophy and possibly stricture formation. The possibility of malignancy in lichen sclerosus et atrophicus of childhood is minimal. The disorder may be reactivated later in life by trauma, pregnancy, or birth control pills. Therapy with topical corticosteroids or testosterone ointment may be helpful. Biyearly checkups after puberty are necessary due to the possibility of malignancy.[24]

Granuloma Annulare

These lesions are asymptomatic reddish-purple nodules arranged in beadlike rings with a depressed center. The lesions may coalesce to form various-shaped plaques. The disorder tends to follow a chronic course, has an association with diabetes, and is more common in females. Extensor aspects of the joints are the sites of predilection. The differential diagnosis includes ringworm, urticaria, lichen planus, and erythema multiforme. Intralesional triamcinolone (5 mg/ml) produces resolution.

Appendix

Common Diagnostic Procedures

A. Fungal Scraping—KOH. The presence of a fungal infection (dermatophyte or *Monilia*) may be confirmed by this microscopic technique. Blistering and scaling lesions can be evaluated.

1. Lightly abrade a scaly area or roof of a vesicle with a #15 scalpel blade.
2. Deposit the material on a slide.
3. Cover with 10–20% potassium hydroxide (KOH) solution and a coverslip.
4. Heat the slide gently for 15–30 seconds.
5. Let the slide cool for 1–2 minutes and press the coverslip to flatten the sample.
6. Examine under the microscope for birefringent fungal hyphae and spores; initially examine with the low-power lens.

B. Fungal Culture. In addition to direct examination, part of the material can be cultured at room temperature in a test tube containing Sabouraud's agar or Dermatophyte Test Medium. Most species of fungus will have a characteristic microscopic appearance in 1–2 weeks.

C. Punch Biopsy. A punch biopsy is a simple procedure to remove sufficient tissue for histopathologic study.

1. Clean an area of a well-matured lesion (except early lesions if blistering disorder) with alcohol.
2. Anesthetize by local intradermal injection of lidocaine 0.5–2% with or without epinephrine.
3. Stretch the skin surrounding the lesion so that it is taut and perpendicular to the wrinkle lines.
4. Rotate the circular punch instrument back and forth ranging from 2 to 8 mm in depth until it penetrates subcutaneous tissue.
5. Grasp the specimen gently with forceps and snip the base with scissors.
6. Place the tissue in 10% neutral buffered formalin.
7. Bleeding can be stopped by application of Monsel's solution, cauterization, or the placement of 4-0 silk or ethilon suture.
8. Sutures should be kept dry and intact for 7–10 days.

D. Wood's Light. Wood's light of 365 nm is helpful in the detection of bacterial and fungal disorders. It may be used in the following situations:

1. Scalp ringworm. Hairs infected with *Microsporum audouini* or *M. canis* fluoresce bright blue-green.
2. Tinea Versicolor. A yellow-golden color is detected on the skin.
3. Erythrasma. This intertriginous infection fluoresces coral-red or pink-orange.
4. Pseudomonas aeruginosa. A yellowish-green color appears due to pyocyanin.[25]

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Legal Rights of Minors 26

Steven R. Smith

Laws concerning pediatric and adolescent obstetrics and gynecology are rapidly changing. Almost every legislative and congressional session and every term of federal court result in debate and modification of the laws affecting adolescent obstetrics and gynecology.

There are several reasons for this level of legal activity. The most fundamental issues of life, human relationships, and values contribute to the high level of legal activity in this area.[1] For example, all of the following play important roles in defining the legal rights of minors to obstetric and gynecologic care: the relationship between a minor and her parents, the definition and determination of what human life means, the right to control one's own body and to make fundamental personal decisions, and a number of religious and moral questions. Moreover, several of the legal principles now central to the definition of the rights of minors are relatively new and not yet well defined. For example, the right of a woman to have an abortion is little more than a decade old.[2] Also, the law is reacting to relatively modern developments such as oral contraceptives and today's earlier maturation.

Although the dynamism of the law in adolescent obstetrics and gynecology is exciting from a legal standpoint, the rapid changes unfortunately make it difficult and confusing for physicians. These changes also make it hard for authors who try to describe legal principles because stable legal principles do not exist.

In this chapter we will first examine the fundamental legal principles and doctrines which underlie issues related to pediatric and adolescent gynecology and then briefly evaluate a number of specific current issues and laws. A few statutes and cases are used to illustrate some approaches to these issues. This chapter does not deal with all of the many legal issues involved in the practice of obstetrics and gynecology generally. For instance, the issue of malpractice or professional negligence is not considered nor are issues related to failed contraception, wrongful birth/wrongful life, genetic counseling, home delivery, experimentation on minors, licensing of practitioners and care facilities, artifical insemination, fetal experimentation, in vitro fertilization, or surrogate mothers. All these topics are fascinating legal issues but are beyond the scope of this chapter.

A caveat: caution must be exercised when applying the statutes or case law of one state to another. It must be remembered also that statutes and regulations are undergoing rapid change as a result of amendments and court decisions. Thus, statutes in force at the time of this writing may not be current now.

Basic Legal Concepts

Several basic common law and constitutional concepts underlie virtually all of the current legal issues and principles concerning obstetric and gynecologic care for minors. In this

section we will briefly consider several of these legal concepts.*

State and Federal Law

State law has traditionally governed the regulation of medical care, the definition of the legal rights of minors, and the relationships between parents and minors. However, federal law recently has played an increasingly important role in these areas because of (1) United States Supreme Court interpretations of the provisions of the Constitution which limit state law (e.g., limit the ability of a state to prohibit abortions); (2) the increasing importance of federal funds in the delivery of health care services and the concomitant regulation of the provision of that care (e.g., Medicaid and federally funded family planning agencies); and (3) Congress's use of federal authority to control interstate commerce to regulate medical care (e.g., drugs and medical devices). While this increasing federal role is important, state law still plays the dominant role in defining and regulating the provision of medical care to minors.†

When state or federal statutes or regulations violate the U.S. Constitution, the Constitution takes precedence, making the statutes or regulations ineffective. When federal law conflicts with state law, federal law ordinarily controls unless the federal law is unconstitutional or permits states an exemption. Thus, the federal constitutional right of privacy invalidates state law prohibiting all abortions; state laws permitting the interstate transportation and sale of illegal oral contraceptives would be ineffective because of federal law.

With the exception of constitutional limitations on a state's right to regulate abortion, contraception, and federal control of drugs and devices, *most* regulation of obstetric and gynecologic care for minors is governed by state law. This means that each state may have its own rules concerning these services and these laws may vary from state to state. In fact, states do differ in what is permitted or required of medical practitioners who provide such services. This makes a clear understanding of the rules of one's own state imperative for the physician. A number of states have statutes or regulations that are unconstitutional in light of recent federal court decisions. Thus, it is also important that the practitioner be aware of federal decisions that may invalidate state statutes and regulations.

The importance of individual state law, the modifications of state law by federal courts, and the speed with which the law is changing make it wise for the medical practitioner to have a continuing relationship with an organization or attorney who can provide current information on state law. Expert legal advice is particularly important in the areas of minor's consent to abortion, confidentiality of information provided by minors, and mandatory reporting laws. (These are discussed later in this chapter.)

The Parent-Child Relationship

At common law children were virtually the property of their parents and thereby subject to parental decisions, direction, and discipline.[3] Children were protected from their own immature judgment by their limited ability both to enter into contracts (except for necessities) and to consent to medical care (except under very limited circumstances).

Throughout this century the concept of parental ownership and control of their children increasingly has come under legal attack. Although parents still have wide latitude in raising their children, minors are now recognized as separate legal entities with their own rights and interests.[4] As a result of these changes, child abuse statutes limit the physical and mental abuse inflicted on children in the name of discipline, and mature minors, despite parental objection, may consent to medical procedures such as abortion.

Although the trend is toward reduced parental control, it is still presumed that

*All references to state and federal law are, of course, related to the United States legal system. Although the broad, general legal principles described in this section have been accepted in other common law countries (e.g., Canada, Great Britain, and Australia), the specific rules regarding minors and obstetric and gynecologic care are not consistent and currently vary considerably even within common law countries.[45,46]

†"Law" is used throughout this chapter to include constitutions, statutes, case law, and administrative regulations and directives.

parents have the right to make most of their children's decisions.

Minors

The law generally considers minors incapable of making binding legal decisions until the age of majority. States define this age differently, although it is usually between 18 and 21. The recent trend, however, has been to lower the age of consent to 18 and to permit some decisions to be made by those even younger.

There have been some common exceptions to the minor's inability to make legally binding decisions. Most common has been the "emancipated minors" rule. Emancipated minors may make legally binding decisions because they are viewed as formally free of the control and responsibility of their parents, usually as a result of marriage, military service, or (in some states) economic independence coupled with parental approval.[5] Some states also have recognized that "mature minors" may make legally binding decisions. The concept of the mature minor is not universally accepted and is somewhat unclear, but it generally refers to those who are able to understand and make complex decisions even though they have not reached the age of majority.[6] The legal tendency, consistent with recent studies of the decision-making ability of older minors,[7,8] is toward giving minors the legal authority to make legally binding decisions at an earlier age.[9,10] In areas such as abortion, the Supreme Court also has indicated a fairly broad authority for mature minors to make their own decisisons.

Consent to Medical Care

Ordinarily, medical care may be provided only if the patient has given consent.[11] This is part of the general right of autonomy, the right to decide for ourselves what will be done to our bodies. When the treatment is important or invasive—surgery, for example—the patient must be informed of the risks and benefits and alternative treatments and their consequences. The patient must give her "informed consent."[12]

One exception is in an emergency where no one is available to give consent.[12] For example, when an adult is unconscious or when a minor has an emergency and there is no family available to give consent, treatment may be undertaken.* State statutes and court decisions have, as we shall see, provided additional exceptions to the usual minor consent rules.

As noted, minors traditionally could not consent to treatment and instead had to depend upon their parents' consent. With the exceptions noted throughout the rest of this chapter, this is still true.[13]

Confidentiality

Physicians have an obligation to respect patient confidentiality. Failure to maintain confidences revealed during treatment may result in civil suits based on negligence or invasion of privacy and may subject the physician to discipline by the licensing agencies. Of course, there are exceptions to this requirement such as when the patient has waived the right to secrecy or where the law specifically permits or requires the physician to release information about the patient.†

It has been assumed that under the common law parents were entitled to any important information about their children. This probably reflects the law today, although because of individual state statutes and the constitutional privacy rights of minors, some possible exceptions in the areas of psychiatric and obstetric and gynecologic care may exist. In many states, however, the right of minors and physicians to withhold information from parents is doubtful or uncertain at best.

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*An additional exception to the requirement of *informed* consent is the so-called "therapeutic privilege." When providing information to a patient which would be quite harmful to the patient, that information may be withheld from the patient, although in many circumstances it should be revealed to others, such as the patient's family.[12]

†The obligation of maintaining confidentiality should not be confused with the existence of a physician-patient privilege.[66] The privilege permits physicians and patients to refuse to reveal, even to courts, the communications that occurred during treatment. Confidentiality is a broader obligation to maintain the secrets of the patient.

Constitutional Privacy

Autonomy Privacy

In 1965, the Surpreme Court in Griswold v. Connecticut first recognized a specific constitutional right of privacy.[14] In *Griswold* the Court struck down a Connecticut statute prohibiting married couples from using contraceptives. The Court noted the private nature of the relationship between the couple and their physician, as well as the intimate relationship between husband and wife. The Court indicated that the constitutional right of privacy protects the right of the individual to make fundamentally important personal decisions without substantial government interference. Among the areas which the Court has identified as fundamentally important and thus protected under the Constitution are procreation decisions, marriage, childrearing, and family life.

Obviously much of the constitutional privacy doctrine directly affects obstetric and gynecologic care because procreation and childrearing decisions are involved. After *Griswold* the Court recognized the constitutional right of unmarried persons to obtain contraceptives without governmental interference.[15] The Court stated if "the right of privacy means anything, it is the right of the *individual*, married or single, to be free from unwarranted governmental intrusion into matters so fundamentally affecting a person as the decision whether to bear or beget a child."[15]

In Roe v. Wade the Supreme Court struck down criminal abortion laws that outlawed abortions except to save the mother's life.[2] The Court noted that such laws interfered with a woman's right of privacy. However, it also held that the right of privacy is not absolute and may be limited if there is a compelling state interest. More recently the Surpreme Court has indicated that the right to have an abortion extends to minors,[10] that a minor cannot routinely be required to have parental permission prior to abortion,[16] and that a minor has the right to at least some kinds of contraceptives without parental consent.[17]

Information Privacy

In addition to autonomy privacy, the right of privacy may include the right to withhold from others certain kinds of private information.[18,19] The extent of this type of privacy is very poorly defined.[20] Thus far the Supreme Court has permitted the state to collect very personal information such as the names of women having abortions as long as it ensures the confidentiality of such information.[16] The right to information privacy may play a future role in determining when a state may require the release of private information about abortions, contraceptives, or other personal matters.[21]

Limitations on the Right of Privacy

Compelling State Interests. The right of privacy may be limited when there is a compelling state interest. In Roe v. Wade the Supreme Court indicated that after the first trimester the state may regulate abortions for the protection of the mother's health. After a fetus is "viable" (able to live outside the mother's body with or without artificial assistance) the state may regulate abortion because it now has a compelling interest in the life of that fetus.[2] Relatively few legitimate compelling state interests can be identified.* Because compelling state interests can overcome fundamental constitutional rights, a broad definition of compelling interest would in effect destroy most constitutional protections. Therefore, there are relatively few interests, such as the protection of life, that a state may use to interfere with privacy rights.[4]

Conflicting Rights. Another potential limitation on minors' rights comes from the conflict between a minor's right of privacy to make procreation and childbearing decisions and the rights of the parents to childrearing privacy rights. Thus far the Supreme Court has tended to favor the procreation decisions of the "mature minor" over the parents' childrearing rights.[16,22] Thus, a state cannot provide blanket authority for a parent to veto an adolescent's decision to have an abortion or to use contraceptives.[10] Nevertheless, the conflict may give the state some latitude in limiting a minor's obstetric and gynecologic care. Some

*Compelling interests may include the protection of human life, preventing violent overthrow of the government, and preserving democracy.[67]

states, for example, may require that parents be informed of the decision of a minor child to have an abortion.[23,24]

Promotion of Privacy Rights. Federal and state governments are not required to promote or encourage the exercise of privacy rights. For example, the federal government may refuse to fund abortions for women through the Medicaid system even though it pays for other forms of obstetric care.[25] However, completely prohibiting the use of a state facility for abortions or sterilizations is more likely to violate the Constitution.[26,27]

State Action and Private Institutions. Private institutions, at least those not so involved with the government as to be thought of as quasi public, have much greater latitude in prohibiting procedures such as abortions and sterilizations. This is because the constitutional right of privacy essentially applies to governmental action. Thus, private hospitals may be able to prohibit abortions or sterilizations if they choose to do so.

Nonsubstantial Burdens on Privacy. To violate constitutional privacy, the government must significantly interfere with the ability of the individual to exercise privacy interests. An incidental or minor impediment is not considered an unconstitutional invasion, even though some particularly sensitive people might object to it. State recordkeeping of abortion information, for example, does not unconstitutionally burden the abortion decision.[16] On the other hand, a state law permitting only pharmacists to sell contraceptives does unconstitutionally burden the individual's right to make fundamental decisions concerning childbearing because it reduces access.[17] The Court has upheld a state requirement that second trimester abortions be done in licensed hospitals (including outpatient hospitals),[28] but it has said that state statutes requiring all second trimester abortions to be performed in general hospitals are unconstitutional.[22,29] No clear line separates the insignificant from the impermissible burden. The mere fact that a state regulation has some impact on obstetric or gynecologic care will not automatically invalidate it.

Minors' Consent to Obstetric and Gynecologic Care

Except in emergencies, as noted earlier, consent must be given prior to medical treatment; unless the risks are minimal some form of "informed" consent is necessary. Physicians providing medical care to minors without parental consent could be held liable in tort (negligence or battery) and run the risk of not being paid for their services.[5] Generally, parents must consent to treatment for their unemancipated children. Some modifications of these general rules have been provided for adolescent obstetric and gynecologic care, however. These have been made by statute in some states and by federal court decisions that affect all states. In addition to the care discussed in this section, emergency care generally can be provided to minors without parental consent and lifesaving care may be undertaken upon the intervention of state social service agencies or courts.[4,30,31]

State Statutes

Some states allow adolescents to consent to some obstetric and gynecologic care, most commonly to treatment for venereal disease, pregnancy, and contraception. Not all states have such statutes, and where they do exist an effort usually is made to limit their scope so that they do not apply to abortion.

These statutes often came about as a result of the recognition, during the 1960s and 1970s, of the increased sexual activity and maturity of adolescents. The movement toward such statutes seems to have abated, and it even may have been reversed so that some states are considering modification or repeal. This may reflect both a change in public attitude and the fact that the courts have implemented some of the policies that the statutes promoted.

The following excerpts from a few statutes illustrate the approaches of several states.

CALIFORNIA

> 34.5 Notwithstanding any other provision of the law, an unmarried minor may give consent to the furnishing of hospital, medical, and surgical care related to the pre-

vention or treatment of pregnancy, and such consent shall not be subject to disaffirmance because of minority. The consent of the parent or parents of such minor shall not be necessary in order to authorize such hospital, medical, and surgical care.

The provisions of this section shall not be construed to authorize a minor to be sterilized without the consent of his or her parent or guardian. . . .

34.7 Notwithstanding any other provision of law, a minor 12 years of age or older who may have come into contact with any infectious, contagious, or communicable disease may give consent to the furnishing of hospital, medical, and surgical care related to the diagnosis or treatment of such disease, if the disease or condition is one which is required by law or regulation adopted pursuant to law to be reported to the local health officer, or a related sexually transmitted disease, as may be determined by the State Director of Health Services. Such consent shall not be subject to disaffirmance because of minority. The consent of the parent, parents, or legal guardian of such minor shall not be necessary to authorize hospital, medical, and surgical care related to such disease and such parent, parents, or legal guardian shall not be liable for payment for any care rendered pursuant to this section.[32]

Colorado

13-22-105 Except as otherwise provided . . . birth control procedures, supplies, and information may be furnished by physicians . . . to any minor who is pregnant, or a parent, or married, or who has the consent of his parent or legal guardian, or who has been referred for such services by another physician, a clergyman, a family planning clinic, a school or institution of higher education, or any agency or instrumentality of this state or any subdivision thereof, or who requests and is in need of birth control procedures, supplies, or information.

13-22-106 (1) Any physician licensed to practice in this state, upon consultation by a minor as a patient who indicates that he or she was the victim of a sexual assault, with the consent of such minor patient, may perform customary and necessary examinations to obtain evidence of the sexual assault and may prescribe for and treat the patient for any immediate condition caused by the sexual assault.

(2) (a) Prior to examining or treating a minor pursuant to subsection (1) of this section, a physician shall make a reasonable effort to notify the parent, parents, legal guardian, or any other person having custody of such minor of the sexual assault.[33]

Florida

381.382 (5) (a) Maternal health and contraceptive information and services of a nonsurgical nature may be rendered to any minor by persons licensed to practice medicine . . . as well as by the department of health and rehabilitative services through its family planning program, provided the minor:

1. Is married,
2. Is a parent,
3. Is pregnant,
4. Has the consent of a parent or legal guardian, or
5. May, in the opinion of the physician, suffer probable health hazards if such services are not provided.

(b) Application of nonpermanent internal contraceptive devices shall not be deemed a surgical procedure.[34]

Kentucky

214.185 (1) Any physician, upon consultation by a minor as a patient, with the consent of such minor may take a diagnostic examination for venereal disease, pregnancy, . . . and may advise, prescribe for, and treat such minor regarding venereal disease . . . ,contraception, pregnancy, or childbirth, all without the consent of or notification to the parent, parents, or guardian of such minor patient, or to any person having custody of such minor patient. Treatment under this section does not include inducing of an abortion or performance of a sterilization operation. In any such case the physician shall incur no civil or criminal liability by reason of having made such diagnostic examination or rendered such treatment, but such immunity shall not apply to any negligent acts or omissions. . . .

(5) The professional may inform the parent or legal guardian of the minor patient of any treatment given or needed where, in the judgment of the professional,

informing the parent or guardian would benefit the health of the minor patient.

(6) Except as otherwise provided in this section, parents, the cabinet for human resources, or any other custodian or guardian of a minor shall not be financially responsible for services rendered under this section unless they are essential for the preservation of the health of the minor.[35]

TEXAS

35.03 (a) A minor may consent to the furnishing of hospital, medical, surgical, and dental care by a licensed physician or dentist if the minor: . . .

(3) consents to the diagnosis and treatment of any infectious, contagious, or communicable disease which is required by law or regulation adopted pursuant to law to be reported by the licensed physician or dentist to a local health officer;

(4) is unmarried and pregnant, and consents to hospital, medical, or surgical treatment, other than abortion, related to her pregnancy;

(b) Consent by a minor to hospital, medical, surgical, or dental treatment under this section is not subject to disaffirmance because of minority. . . .

(d) A licensed physician or dentist may, with or without the consent of a minor who is a patient, advise the parents, managing conservator, or guardian of the minor of the treatment given to or needed by the minor.

(e) A physician or dentist licensed to practice medicine or dentistry in this state or a hospital or medical facility shall not be liable for the examination and treatment of minors under this section except for his or its own acts of negligence.[36]

Consent to Contraception

In 1977, in *Carey* v. *Population Services*,[17] the Supreme Court held that the right of privacy includes the right of minors to have access to some contraceptives. It struck down a New York statute that limited access by minors under 16. Therefore, a state may not completely prohibit the use nor availability of nonprescription contraceptives to minors.[37] This is an exception to the general requirement of parental consent. (The issue of whether a state may require that parents be informed of their child's use of contraceptives is another matter and discussed below.)

Informed consent to the use of IUDs and other prescription drugs and FDA-controlled devices should be obtained from the adolescent and, if required by state law, her parents. The constitutional right of a mature minor to prescription contraceptives without parental consent is not clear. However, it is likely that minors who can demonstrate "maturity" (competence) would not be required to have their parents' permission to use contraceptives. As always, practitioners must provide reasonable information about the benefits and risks of the proposed treatment and about contraceptive alternatives.

Consent to Abortions

Since the *Roe* v. *Wade* decision many states have tried to limit abortions by imposing a variety of fairly restrictive consent and other requirements. The federal courts have ruled many of these unconstitutional.[38] The states have then tried other approaches. The process is something of a cat and mouse game. In the summer of 1983, the Supreme Court handed down a number of opinions that appeared to indicate that it was serious about protecting the right to abortion. However, because the Court upheld a number of state statutes that somewhat limited access to abortion, its 1983 decisions may actually encourage states to make access to abortions more difficult, particularly for minors.

In 1976, in *Planned Parenthood* v. *Danforth*,[16] the Court held that the right of privacy to decide to have an abortion extends to minors, and the state does not have the constitutional authority to delegate to a third party the decision of a "competent and mature minor" to have an abortion. In *Bellotti* v. *Baird*[10] the Court held that a state statute permitting a judicial veto of mature minor's decision to have an abortion was unconstitutional. The statute allowed the state courts considerable latitude in deciding whether to consent to the abortion.[39] In the summer of 1983, the Court held unconstitutional an ordinance that provided that all minors under 15 were too immature to make abortion decisions.[22] But in *Planned Parenthood Assocation of Kansas City* v. *Ashcroft*[29] the Court upheld a state statute

requiring all minors to obtain either parental or judicial consent for an abortion. This statute was constitutional because the state courts were *required* to give consent to the abortion if the minor was mature enough to make the decision or if the abortion was in her best interest. (The state statute exempted emancipated minors from the judicial consent requirement.) The five justices who supported the decision apparently believed that it imposed no "undue burden on any right of a minor who may have to undergo an abortion" or that it was necessary to protect immature minors.

On the same day, the Supreme Court upheld an ordinance requiring informed consent prior to an abortion but struck down as unconstitutional the ordinance which specified that prior to performing abortions physicians disclose information regarding the fetus. Such information included a description of the features of the fetus, a list of possible complications, and the opinion that life begins from the moment of conception.[22] This was a kind of "shock" informed consent.[40]

The fact that a state is constitutionally *permitted* to require judicial or parental consent does not, of course, mean that it is *required* to pass such a law. However, it is likely that many states will move in this direction. That probably will mean that more states will require parental consent or a court order determining either (1) that the minor is sufficiently mature to make the decision, *or* (2) that the abortion is in the best interest of the minor. States, however, will not be able to require "shock" informed consent or call for waiting periods between the time of consent and abortion.

The Court's opinion that the requirement of judicial approval prior to abortion will not make it unduly difficult for a minor to have an abortion is unrealistic and unlikely to improve health care. In fact, such laws probably will reduce and restrict—and may be intended to do so—the availability of abortions to adolescents and the practice of obstetricians and gynecologists. Professionals treating pregnant minors in states requiring parental or judicial consent may find it necessary to establish a method to assist them in obtaining judicial consent to abortion.

Abortion is definitely a significant medical procedure, and informed consent is essential.

Except in the most extraordinary circumstances, an abortion should not be done when the minor objects and then only with court approval.

Other Medical Procedures

There are a limited number of cases that address consent to other obstetric and gynecologic treatments. However, it is likely a court would order consent, even over parental objection, to treatment for contagious conditions such as venereal disease or when a condition is exceptionally harmful or life-threatening.[41]

Confidentiality and the Release of Information

The law may prohibit the release of certain information, require its release, or leave the release to the physician's discretion.[42] The usual obligation of a physician to maintain patient confidentiality is modified when a minor is involved so that parents have access to the information. This section addresses the release of information to parents.

State Statutes

Some states have defined by statute physicians' obligations regarding the release of obstetric and gynecologic information.[43] These statutes vary considerably. Compare, for example, the Colorado[33] statute with sections of the Kentucky[35] and Texas[36] statutes and the New York Public Health Code[44] (all excerpted above).[44]

Most states with specific statutory provisions on the release of contraception and abortion information either permit or require the release of information to parents. The trend appears to be toward requiring its release and even requiring the physician to notify parents when a child requests an abortion or contraceptives.

The Supreme Court has upheld a statute requiring physicians to inform the parents of "immature, dependent" minors who seek abortions.[23,24] It is not clear whether states also could constitutionally require the release of such information to the parents of a mature minor.[46] It should be emphasized that states

are not *required* to pass such laws but merely *permitted* to do so. Thus, physicians are required to notify parents only in states with a specific law (generally a statute).[47]

It is still unclear whether the Court would uphold a similar state statute requiring notification of parents when their "immature, dependent" minors request contraceptives. The best guess is that the Court probably would uphold such a state statute, at least when prescription contraceptives are involved.

Information Privacy of Minors

To date, most court decisions that have involved the release of, or required reporting of, information have been concerned with the degree to which such processes interfere with the right to have an abortion. Another constitutional right of privacy—information privacy—may play a role in future decisions. Information about contraception and abortion is personal and its release would offend many people. The courts, however, may find that the required release of such information is justified on the basis that the state has an interest in promoting intrafamily communications.

"Squeal Rule"

In 1983, the Department of Health and Human Services (HHS) proposed regulations that would have required federally funded birth control clinics to notify the parents of unemancipated minors when the child was given prescription contraceptives.[48] An exception was provided, which is not uncommon in such notification laws: when it was determined that notification would result in physical harm to the minor, the clinics were not required to inform parents. That regulation was struck down by federal courts because it was not authorized by Congress.[49,50] Although the administration decided not to appeal, the issue of whether federally funded centers should be required to provide parental notification is not settled, and the legislative and judicial debate over the "squeal rule" will undoubtedly continue.[51] It should be noted, however, that the proposal is limited to federally funded family planning clinics and does not extend to private practitioners or clinics not funded by the federal government. Some states might, however, try to impose a broader "squeal rule" that could apply to private clinics.

A Practical Note

The purpose of parental notification rules, according to HHS and some courts, is to encourage parents to counsel their pregnant or sexually active children and help them through a difficult time. Such a view appears to assume that all American families are accurately represented by Norman Rockwell paintings. Many times, in fact, notifying the parents only increases family problems. Some clinics have, therefore, steadfastly refused to inform parents of their children's treatment. It remains an open question whether such a position can be maintained in the face of specific state or federal laws requiring notification.[52]

In jurisdictions requiring parental notification for certain types of obstetric and gynecologic care, the practitioner should inform minors at the beginning of treatment of this reporting requirement. This is another area where significant changes may be expected over the next several years, and particularly careful monitoring of changes in federal, state, and local law is important.

Even where parents have a right to their child's medical records, practitioners need not seek parents out to inform them of the therapy. Often parents do not know their child is being treated. Of course, when parental consent is needed the parents must be involved, although they can agree as part of the consent that they will not request information revealed during treatment.

When the right of parental rights to information is unclear, practitioners could choose to refuse to release the information without a court order or determination that the information must be released. If the release of information to parents is optional, physicians usually should do so only when it is in the best interest of the minor. Ordinarily the minor should be told that the information is being released.

Practitioners also may be asked to release information to an insurance company or

other third party for payment of services. In such instances, that information should be released only with the consent of the patient or a minor patient's parents.

Mandatory Reporting Laws

In a limited number of circumstances practitioners are required by law to report certain diagnoses or findings to state authorities. Failure to do so may be a criminal offense and may lead to civil liability.

Reporting statutes vary from state to state, but the obligation to report child abuse and infectious venereal diseases is common. Some states require that records be kept or that reports be made to state authorities concerning abortions, certain prescription drugs, miscarriages, or infant deaths.

Child Abuse

All states require that child abuse be reported,[53] although statutes vary from state to state.[54] The Colorado statute, excerpts of which are reprinted below, is a fair representation of the scope of many state statutes.[55]

COLORADO

19-10-103 As used in this article, unless the context otherwise requires:

(1) (a) "Abuse" or "child abuse or neglect" means an act or omission in one of the following categories which seriously threatens the health or welfare of a child:

(I) Any case in which a child exhibits evidence of skin bruising, bleeding, malnutrition, failure to thrive, burns, fracture of any bone, subdural hematoma, soft tissue swelling, or death, and such condition or death is not justifiably explained, or where the history given concerning such condition or death is at variance with the degree or type of such condition or death, or circumstances indicate that such condition or death may not be the product of an accidental occurrence;

(II) Any case in which a child is subjected to sexual assault or molestation, sexual exploitation, or prostitution;

(III) Any case in which the child's parents, legal guardians, or custodians fail to take the same actions to provide adequate food, clothing, shelter, or supervision that a prudent parent would take.

(b) In all cases, those investigating reports of child abuse shall take into account accepted child-rearing practices of the culture in which the child participates. Nothing in this subsection (1) shall refer to acts which could be construed to be a reasonable exercise of parental discipline. . . .

19-10-104 (1) Any person specified in subsection (2) of this section who has reasonable cause to know or suspect that a child has been subjected to abuse or neglect or who has observed the child being subjected to circumstances or conditions which would reasonably result in abuse or neglect shall immediately report or cause a report to be made of such fact to the county department or local law enforcement agency.

(2) Persons required to report such abuse or neglect or circumstances or conditions shall include any [medical or mental health professional].

(3) In addition to those persons specifically required by this section to report known or suspected child abuse or neglect and circumstances or conditions which might reasonably result in child abuse or neglect, any other person may report known or suspected child abuse or neglect to the local law enforcement agency or the county department.

(4) Any person who willfully violates the provisions of subsection (1) of this section:

(a) Commits a class 3 misdemeanor . . .

(b) Shall be liable for damages proximately caused thereby.[33]

Note the broad definition of abuse and neglect in the Colorado statute. A number of states now require that emotional or mental abuse also be reported.[56] Sexual assault or molestation is specifically included. In addition, abuse must be reported when it is known or *suspected* and in cases where conditions would reasonably be expected to result in abuse or neglect.[57]

Most states provide immunity agains liability for those who report cases of suspected child abuse.[53,54]

Venereal Disease Reporting Statutes

States commonly require that professionals report cases of venereal disease to a state or

local board of health. The portion of the Iowa statute below is typical.

IOWA

> 140.4 Immediately after the first examination or treatment of any person infected with any venereal disease, the physician performing the same shall transmit to the state department of health a report stating the name, age, sex, marital status, occupation of patient, name of the disease, probable source of infection, and duration of the disease; except, when a case occurs within the jurisdiction of a local health department, such a report shall be made directly to the local health department which shall immediately forward the same information to the state department of health. Such reports shall be made in accordance with rules adopted by the state department of health. Such reports shall be confidential. Any person in good faith making a report of a venereal disease shall have immunity from any liability, civil or criminal, which might otherwise be incurred or imposed as a result of such report.[58]

As with the child abuse reporting statutes, failure to report cases may subject the professional to criminal prosecution. A report made in good faith is immune from liability.[54]

Payment for Services

Under common law a minor could not be held to contracts except for necessities, and a parent was obligated to provide the fundamentals of life. Thus, in most cases, a parent is required to pay for the minor's medical services, but if a minor contracts for necessary medical services the minor can be held to that contract.

It is not uncommon for states that permit minors medical treatment without parental consent to provide that parents are not financially responsible for treatment to which they did not consent (e.g., see the Colorado, Kentucky, and Texas consent statutes reprinted above). Ordinarily the minor would be responsible for paying for such services.[41]

Involuntary Sterilization

Permanent sterilization of competent minors generally should not be undertaken unless it is necessary to save a life or is incidental to other essential treatment. Some states by statute specifically do not allow minors to consent to sterilization.[59]

A troublesome question has been whether it is appropriate for minors to be sterilized when the parents or guardians consent. Sterilization is usually sought because profoundly incompetent female minors are unable to understand their own sexuality and the consequences of sexual contact. Moreover, they would be unable to care for any children they might bear. On the other hand, courts are reluctant to remove the fundamental right to procreation and are concerned about the potential for abuse.[60]

Courts are permitting some limited sterilization of profoundly incompetent minors after a process to determine that such a step is justified. This usually follows a formal hearing during which a guardian *ad litem* (for this legal process) is appointed for the minor. If she is judged to be permanently incompetent because of profound mental deficiency and it is determined that sterilization is in her best interest, the court may approve the procedure.* Even in the absence of express statutory authority, some courts have utilized their "inherent" judicial authority to order sterilization.[61] These court-ordered sterilizations are appropriately limited to a narrow group of severely mentally retarded minors.[62]

Participation in the Legal System

It is important that practitioners treating pediatric and adolescent patients participate in the legal system to promote rational rules for the obstetric and gynecologic care of these patients. Sensible reform in the areas of minors' consent, parental notice of obstetric care, confidentiality of treatment, and involuntary sterilization depends upon the participation of physicians who understand the medical issues and are willing to share their expertise with lawmakers.

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*Ordinarily a physician performing a sterilization pursuant to a court order can do so without incurring civil liability. Where the court issuing the order does not have authority to do so, it is possible that the physician will be liable. This has led one expert to suggest some caution in implementing these orders.[41]

Commentary

The current law would be more fair and compassionate if it were more realistic about the ability of older minors to consent to treatment. Adolescents 14 and older—except for those who are not mentally competent—should be permitted to consent to most forms of medical treatment. Even without a general minor consent law, states should adopt laws permitting minors to consent to treatment for pregnancy, contraception, abortion, and venereal disease. The Supreme Court's recent decision, which apparently permits states to require that minors seeking abortions be judicially determined competent, is both unrealistic and likely to be a real burden to many minors. States should avoid adopting statutes requiring such determinations.

The confidentiality of the adolescent-physician relationship should be respected. Minors seeking contraceptive advice, treatment for venereal disease, or abortions should be urged to confide in their families, and the substantial majority do.[63] But the decision of whether to involve parents should be left to the adolescent. Parental notification statutes should not be adopted.

There is a significant price paid for required parental consent or notification. One study estimates that had there been a parental notice requirement in 1978, approximately 125,000 minors using family planning agencies would have stopped using effective methods of contraception. This would have resulted in 33,000 additional pregnancies, leading to 14,000 abortions, 9000 out-of-wedlock births, 6000 forced marriages, and 4000 miscarriages. A parental notice requirement for abortions would have meant that 42,000 minors would not have had legal abortions, the result of which would have been 19,000 illegal abortions, 18,000 unwanted births, and 5000 runaways.[63] These figures are speculative, but they do indicate the magnitude of the problem presented by parental notification laws. Restricting the rights to abortions and contraception may injure the weakest members of society.[64]

State reporting statutes can serve an important social function in eliminating and preventing disease and injury. It is essential, however, that the confidentiality of reports be maintained. It is equally essential that the statutes be reasonably narrow and clear; some child abuse statutes are broad to the point of being vague. Such breadth may defeat the purpose of the statute.

The law should recognize the ability of most "mature" minors to make treatment decisions and realistically face the fact that the lack of communication between some parents and their teenagers makes it difficult for these issues to be discussed openly.

Summary

Laws concerning pediatric and adolescent obstetric and gynecologic care are rapidly changing. It is reasonable to expect continued change in these areas of the law. This dynamism makes it difficult for those who practice in the area. Thus, practitioners should establish a relationship with an organization or attorney who can keep them abreast of the current law.

There are a number of important basic concepts which underlie the current legal issues concerning care for minors. While the federal government is increasingly becoming involved, the individual states still play the dominant role in defining and regulating the legal rights of minors and the relationships between parents and their minor children. Therefore, rules concerning the provision of medical care to minors vary somewhat from state to state.

Although the absolute control of parents over their children has been reduced, there still is a strong presumption that parents may make most decisions for their minor children. Minors generally are considered incapable of making binding legal decisions. States define the age of majority between 18 and 21 years.

Medical care usually may be provided only with the patient's consent. When dangerous or invasive procedures are involved, "informed" consent is an essential part of the treatment. Physicians have an obligation to maintain the confidences revealed during treatment. However, parents ordinarily are entitled to information about the medical treatment their children receive.

The U.S. Supreme Court has recognized a specific constitutional right of privacy that

includes the right to make procreation and childrearing decisions. This right includes the right to use contraceptives regardless of marital status or age. It also includes the right to abortion. However, the right of privacy is not absolute and may be limited when there is a compelling state interest (e.g., protection of human life).

Although minors generally must have parental consent for medical treatment, some states have statutes which permit minors to have obstetric and gynecologic treatment without parental consent. The Supreme Court also has held that minors have a right to contraceptives and abortions. The Court has, however, permitted states to require that the minor prove she is sufficiently mature to make the decision regarding abortion. The parental consent rule regarding contraception and treatment for venereal disease also has been somewhat modified by statute in some states. The Supreme Court upheld a state statute requiring physicians to inform the parents of "immature, dependent" minors when their daughter seeks an abortion. Whether states could also require such information to be provided to parents of mature minors is not yet clear.

The Department of Health and Human Services proposed that federally funded birth control clinics be required to notify the parents of unemancipated minors when their children were provided prescription contraceptive "drugs or devices." Federal courts have prevented this rule from going into effect, and the debate over the degree to which parents be informed of the decision of their children to use contraceptives will undoubtedly continue.

In some instances practitioners are required to inform the state of certain diagnoses or findings. Failure to make these reports as required by law may be a criminal offense and may lead to civil liability. The most common reporting statutes involve child abuse and venereal diseases. All states require that child abuse, often very broadly defined, be reported to state authorities. States commonly require that professionals diagnosing venereal disease make reports to a state or local board of health. In addition, some states have a variety of other reporting statutes requiring record-keeping concerning abortions, prescription drugs, and fetal deaths.

A number of states that permit minors to consent to medical treatment without parental consent also provide that the parents are not financially responsible for medical treatment to which they do not consent. Ordinarily the minor would be responsible for such services.

States do not permit minors to consent to irreversible, permanent sterilization. Sterilization is sometimes sought for the profoundly incompetent (mentally retarded). There is potential for serious abuse of permanent sterilization, and generally it is permitted only after a hearing at which the minor is represented by a guardian *ad litem*, and only when the mental incompetency is profound and permanent and where sterilization clearly appears to be in the best interest of the incompetent.

The rapidly changing laws governing the practice of pediatric and adolescent obstetrics and gynecology are a challenge to practitioners. Physicians today have the opportunity to mold and improve the law. Legislative bodies, administrative agencies, and courts urgently need the expertise, advice, and assistance of knowledgeable physicians to help develop just, compassionate, and effective legal principles.

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Index