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Preface
Adolescent reproductive endocrinology

Ann J. Davis, MD
Guest Editor

I am thrilled that this collection of articles on adolescent reproductive endocrinology is being republished for the *Obstetrics and Gynecology Clinics of North America*. These articles first appeared in the January 2003 issue of the *Infertility and Reproductive and Medicine Clinics of North America*. Each article's author(s) have extraordinary expertise, which is important to share in published form. Sometimes adolescent reproductive endocrinology is seen as a "sub-sub-specialty." In actuality it encompasses many basics of gynecology (such as communication, normal puberty, polycystic ovarian syndrome). This foundation of knowledge allows us to address many of the more complex molecular issues and clinical scenarios, which are also addressed within this volume of the *Clinics*.

I hope you find that adolescent reproductive medicine is fascinating and that the information in these articles is useful in your clinical practice. The subjects covered encompass a wide array of topics.

Providers who deliver care in this field must have excellent communication skills and be well versed in everything from adolescent psycho-social issues to surgery to molecular biology. This issue begins with an excellent article by Drs. Bacon and Burgis on the age old challenge of communicating with this special and unique age group. At the other end of the spectrum Drs. Gracia and Driscoll describe the molecular basis of pubertal abnormalities in their up-to-date article.

New information on onset of puberty is discussed by Drs. Lalwani, Reindollar and Davis in the article on normal onset of puberty. Contemporary issues in primary amenorrhea and Turner syndrome are discussed in separate articles by Drs. Timmreck, Karnis, and Reindollar.

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Drs. Strickland and Wall attack one of the most common clinical problems in adolescent gynecology, abnormal uterine bleeding, with great clarity. The controversies and new treatment options for patients with polycystic ovary syndrome are discussed eloquently by Drs. Pfeifer and Dayal. Eating disorders which often present to gynecologists as menstrual disorders or abdominal pain are detailed in a succinct and well thought out manner by Dr. Rome.

Other common adolescent reproductive problems rounding out this issue include an excellent and practical discussion of adolescent endometriosis by Drs. Attaran and Gidwani. The array of topics is finalized by a thoughtful article on common controversies in adolescent hormonal contraception by Drs. Anne R. Davis and Teal.

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Communicating with the adolescent gynecology patient

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Communicating with the adolescent gynecology patient

Most health care providers agree that adolescence is a time of great change. Maintaining a healthy dialogue with teenage patients requires time, patience, and skill. To establish credibility, a health care provider must establish trust, maintain confidentiality, and provide patient education in a concise, understandable way. Teens view health care providers as a credible source of information, thus giving teen providers a unique opportunity to impact the health of their patients for many years [1,2].

As teens develop physically, they grow psychosocially. With physical maturity, teens move away from the concrete thinking of childhood and begin to think abstractly. These stages of development were outlined by Piaget and must be considered by those who care for teens [2–4] (Table 1). Early adolescents (ages 12–14) still think concretely, so it is important to keep explanations short and to the point. Simple definitions and reassurance usually go a long way in opening up conversation.

Middle adolescents (ages 15–17) develop abstract thinking. This age group is most likely to be involved in risk-taking behavior, and is most influenced by their peers. Interview skills in this group revolves around open-ended questions and role playing, where the teen can state what she would do in certain situations.

Older adolescence (ages 18–21) marks the transition to adulthood. These teens can fully appreciate their action and the consequences. They need guidance but must also understand that they make their own health care decisions.

Effective caring for adolescents hinges on trust. Teens respond to health care providers who have a relaxed, confident attitude. Eye contact is a must, and a personal interest in what they are involved in helps to establish a two-way dialogue

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Table 1
Stages of adolescence

Stage	Developmental characteristics
Early (12–14 yrs)	Period of pubescent growth and maturation
	Youngsters retain concrete thinking and conformist mortality of childhood
	Begin to separate from parents and identify with peers
Middle (15–17 yrs)	Moral choices begin to be based on abstract values
	Youngsters can imagine future consequences of their actions but cannot fully assess them
	Peer influences often override internal sense of right and wrong
	Risk-taking behaviors increase
	Preoccupation with body image affects health-related choices
	Conflict with parents is at its peak
Late (18–21 yrs)	Formal operational thinking develops, along with a fuller appreciation of the consequences of actions
	The individual has developed a set of personal values that govern choices
	May accept parental values or develop own

From Alderman EM, Fleischman AR. Should adolescents make their own health care choices? Contemporary Adolescent Gynecology 1996;2:5–14; with permission.

[2]. The authors usually ask teens about school activities and their friends. This easily allows us to assess maturity and peer group influences. Open-ended questions and "what would you do if" questions work best to assess risk-taking behavior. For example, a 15-year-old might say that she understands the risk for pregnancy with unprotected intercourse. When asked to advise a friend who was considering unprotected sex, however, she might respond that pregnancy was not a risk the first time. This line of questioning also helps providers assess knowledge. Teens appreciate a good listener; be genuine, not parental. Remember not to lecture. Try to limit explanations to a minute or less [1,2]. This can be hard to do when explaining a complex situation, such as premature ovarian failure, but it can apply to most situations. The authors like to use a combination of written and verbal instructions. Some teens remember best with written instructions, but they may be reluctant to take them home. An example of this relates to starting oral contraceptives. The authors give written instructions knowing that they may never make it past the trash can in our offices and back up the written instructions with a visual demonstration using a sample pack of pills that the teen will actually take with her.

First office visit

The first gynecology office visit for a teen usually anxiety-filled. Some guidelines for the teen gynecology visit can turn this into an educational, trust-building relationship that can positively affect teen behavior. The initial interview should be conducted confidentially and with the teen fully clothed. It is preferable that the interview and exam not be interrupted [3,4]. One strategy for this is to schedule teens in a "special office time" and instruct the staff not to interrupt. The authors use one afternoon a week exclusively for teens. This is an afternoon

when the authors are not on call and can have a "no interruptions" rule. The teen's first visit is the best opportunity to learn all one can about her home situation, her relationship with her parents and peers, and her school situation. Interruptions compromise your ability to gather this information.

Confidentiality

The importance of confidentiality cannot be overstated. Teens need confidentiality to get the health care they deserve. The authors usually begin teen interviews with the teen and her mother. Mothers can usually provide accurate historical data. This is especially useful with younger teens [4]. With the mother in the interview, confidentiality is addressed up front. Many parents are eager for their teen to develop a good relationship with a health care provider. Most parents, who are worried about what is discussed without them, do feel that confidentiality is in the best interest of their teen. The authors usually tell the mother and the teen together that the teenage years are the years when teens can decide to do many things for the first time. This is the time when many teens decide to smoke, drink alcohol, use drugs, have sex, or not to do any of those things. The authors explain that our goal is for them to make informed, thoughtful decisions and not decisions that will adversely affect them for years to come. The teen and her mother are told that the patient's chart is confidential although it is made clear that confidentiality does not extend to life threatening behaviors. Some examples of those situations are given, such as diagnosis that requires surgery [2,4]. The mother is informed that her teen will receive information about teen sexuality, healthy eating, exercise, STDs, and contraception. Brochures are provided to each teen at her first visit. A business card with the office phone number is included and the teen is encouraged to call with questions and problems.

After a history and confidentiality explanation, the mother is asked about her concerns and expectations for the visit. The parents' concerns are often different from that of the teen. The mother is then excused from the room. Questions about sexual activity and other risk taking behaviors are asked in private (Box 1). Teens are always encouraged to talk to their parents about what they are doing or thinking about doing. Peer group influence is assessed by using role-playing. Peer groups can be a strong, positive influence [4]. One teen told the authors that her friends would not consider sexual activity or the use of alcohol while they were in high school.

The private portion of the interview is also used to go over the physical exam in detail. Teens sometimes say that they know all about their anatomy, but on reviewing this with models, any misconceptions can usually be cleared up. The use of diagrams and pictures can help teens understand disease processes more clearly. The physical exam is tailored to the needs of the teen. A 13-year-old who has irregular bleeding without any other abnormalities needs a very different exam than a 15-year-old who is sexually active. When discussing the physical exam, acknowledging anxiety usually helps put the teen at ease.

Box 1. Gaining the trust of adolescent patients

Be relaxed, make eye contact
Be genuine, friendly, and open
Demonstrate respect and positive regard
Be interested in the patient's needs, questions, and activities
Address confidentiality issues
Inquire about the patient's concerns
Understand that full trust may take time
Be an authority, not authoritarian
Be nonjudgmental
Ask the hard questions!

Data from: American College of Obstetricians and Gynecologists. Primary and preventive care with periodic assessments. ACOG Committee Opinion 246. Washington, D.C., ACOG 2000

Some teens want their mothers in the room during the physical exam; the teen is asked about this in private. This helps the teen express her true wishes without fear of hurting her mother's feelings [4].

Asking teens and moms separately and together about their expectations for the office visit can also expose the ''hidden agenda''. The mother may want her daughter to have relief from painful periods, whereas the teen is worried about a sexually transmitted disease. Occasionally a parent has a hidden agenda, but they are more common in teens [2].

The interview should involve sexuality and not just the facts about STDs. Most teens today have factual knowledge about STDs, but they would like more discussion in many areas of sexuality (Table 2).

Teens need to talk with their physicians about sex. This is a perfect time to ask open-ended questions and ''what if'' situations. Remember that the questions need to be tailored to the age of the teen. A 14-year-old may be considering sex, but is unable to discuss it directly. By asking a question about a girlfriend's sexual

Table 2
Discussing sexual issues: wish versus reality

Topic	Teens' interest	Frequency of actual discussion
STDs	70%	18%
Contraception	66%	22%
Menses	55%	49%
Sexual functioning	53%	24%
Sexual abuse	36%	6%
Secondary sexual characteristics	50%	23%

Data from Malus M, LaChance PA, Lamy L, et al. Priorities in adolescent healthcare: the teenager's viewpoint. J Fam Pract 1987;25:159.

behavior, you may help her discuss what she is considering. You may also uncover misconceptions that she has about sex, pregnancy risk, and contraception. Do not automatically assume that a teen is heterosexual. Many teens are working through gender identity issues, and an open discussion can follow disclosure of this [2,4].

Most teens need to improve their communication skills when it comes to sexuality. Role-playing may help. Many teens know where to buy condoms, but they may not know how to use them or what to say to a partner who refuses to use one. Rehearsing this situation can be very helpful [2].

The physical exam can also be used as a time to teach and explain. The authors tell our patients what is normal and what is not. At the end of the exam, the authors review what we have discussed and decided with the teen. The teen is asked permission to share the information with her mother. An offer is made to facilitate discussion of any topics that the teen has been unable to discuss with her mother [2,4].

Discussion topics in adolescent health

Comprehensive adolescent healthcare may be provided by physicians in several specialties, including obstetrics and gynecology. Some female patients

Box 2. Pertinent history and exam of adolescents

History

- Chief complaint
- Medical, surgical, and family health history
- Medications and food supplements
- Smoking, drug, or alcohol use
- Personal safety (seat belts, guns)
- Sexual activity
- Immunizations

Examination

- Weight, height
- Blood pressure
- Pubertal development (Tanner staging)
- Pelvic exam (if indicated)
- Skin screening

Data from: American College of Obstetricians and Gynecologists. Primary and preventive care with periodic assessments. ACOG Committee Opinion 246. Washington, D.C., ACOG 2000.

are referred from male primary care providers to obstetrician/gynecologist at or around puberty to assist in the transition to adult female healthcare.

Primary care specialties addressed the need for screening healthcare for women ages 13 to 19. The 2002 guidelines from the American College of Obstetricians and Gynecologists list these grouped by history, exam, and psychosocial issues. These are summarized in Boxes 2 and 3 [5]. These needs should prompt healthcare providers to discuss a variety of topics with their teen patients. Decide on a course of management and develop future goals. This can

Box 3. Psychosocial issues for adolescent health

Sexuality

current sexual activity
sexual orientation
STD risk
pregnancy prevention

High risk behaviors

Alcohol
Smoking
Drugs
Firearms
Seatbelts
Recreational activities

Preventive healthcare

Hygiene
Exercise
Diet - nutrition
Food supplements

Relationships

Friends
Family
School experience
Goal development
Depression, anxiety

Data from: American College of Obstetricians and Gynecologists. Primary and preventive care: periodic assessments. ACOG Committee Opinion 246. Washington, DC, ACOG 2000.

assist with building patients' confidence and can provide clues about progress or stumbling blocks. Addressing additional topics such as school progress, after school activities, hobbies, and relationship development allow good introduction to the topics of emotional health, risk-taking behavior, sexual identity, and sexual activity. Your genuine interest and inquiry about topics of importance to your patients fosters future confidence in your judgment and understanding.

When some of these sensitive topics are initially presented, some teens may not make eye contact or may require several visits to feel comfortable enough to have a discussion in these areas. Even if no answer is initially illicited, teens will be glad that their physician is willing to discuss these topics.

Box 4 contains suggested topics to raise for discussion.

In cases where information that the physician may not be able to completely manage is discovered, referral sources must be readily identified along with offers to arrange services for the teen. Provision of written materials or suggested internet sites with reliable, accurate information, may be recommended for later perusal.

- When introducing these topics, several interview techniques may be helpful:
- Remain objective and avoid judgments
- Watch your verbal responses and body language
- Avoid note taking, make eye contact
- Use open-ended questions
- Guide the conversation toward patient information
- Encourage communication with a parent or trusted adult.
- When conversations become lengthy, try to address all of the issues pertinent to the present visit or any emergency needs. Emphasize how important other topics may be and arrange a follow-up time to approach these problems. Some practices have a ''phone hour'' or an e-mail time. Teens may take advantage of these groups of discussions since privacy may be more assured.

Box 4. Topics to discuss with teens

Sexually transmitted diseases
Acne
Weight
Contraception
Sexuality/sexual orientation
Sexual satisfaction
Physical or sexual abuse
Function of sexual organs
Cancer fears
Menses
Self-esteem
Personal goals

Box 5. SAFE TIMES mnemonic

S sexuality physiology, personal activity, contraception
A affect, abuse depression screening
F family family support, medical history
E exam exam anticipated, self-exam of breast or genitals
T timing developmental milestones
I immunizations immunizations
M minerals nutrition
E education, employment current progress and goals
S safety vehicles, substances, guns

The health care provider should note differences in the frequency of visits. Pediatricians may recommend health maintenance visits only once every 2 to 3 years during adolescence. For sexually active teens or those with gynecologic problems or prescription medications, visits must be considered more frequently, or at least once a year. The expected procedures during each visit, including pelvic exams, blood work, or other testing, should be outlined for the teen.

To cover topics in a methodical fashion, one physician recommended the SAFE TIMES screening mnemonic (Box 5) [6].

Physicians may wonder if their efforts are useful or taken seriously. An enthusiastic "yes" is supported by the literature!

As discussed earlier, frank conversations with a parent or trusted adult should be encouraged. The literature also supports the benefit of these interactions. In the area of sexuality, for example:

- Less frequent parent/adolescent communication is associated with less contraceptive use, lower self efficacy to negotiate safe sex, and less communication between adolescents and their sex partners [7].
- Adolescents who live with their mothers in a perceived-supported environment, reported more communication with sex partners about sexual risks and protected sexual encounters with a steady partner [8].
- Close relationships with supportive parents also seem to be related to later onset of sexual activity and improved contraceptive use [9–11]. Conflicted relationships with adults may provide the opposite effects [11].

Making your office adolescent-friendly

Setting adolescent patients at ease may be facilitated by the use of appropriate written materials, videotapes, or a computer center that provides suggested websites for teens while waiting or after the visit. These sites may be provided to the teen for home use, as well. Let each teen patient know how to reach the office staff if they have any confidential questions. Make sure that there is a

Box 6. Websites that address issues in sexuality and reproductive health regarding teens:

ARHP Patient Education Site: http://www.arhp.org/arhpframepated.htm
Center for Young Women's Health:http://www.youngwomenshealth.org
Emergency Contraceptive Site: http://www.not-2-late.com
Teenwire: http://www.teenwire.com
It's Your (Sex) Life: http://www.itsyoursexlife.com
Sex, Etc.: http://www.sxetc.org

mutual understanding of topics, which may be kept confidential, and that the office staff similarly informed. Many offices are tempted to provide written materials in the waiting area. Teens are often reluctant to select brochures with sensitive topics because they do not wish their parents, adults, or other patients in the waiting room to see which pamphlets they select. Placing these brochures in the examination room may improve the teen's comfort level in accessing this information. The healthcare provider may also issue brochures.

Many excellent videos are available in the areas of contraception, contraceptive compliance, sexuality, menstrual hygiene, and even anger resolution and conflict management within relationships. Setting aside a small room for patient viewing with a selection of videos available, may facilitate the conversations that are initiated by the healthcare provider.

Because many teens have access to computers at home, a listing of helpful websites may also serve to emphasize information provided in the office (Box 6).

For physicians who serve adult and teen populations, using these suggestions may allow assistance for the teen patient without any disruption to general office practice. Attempts should be made to schedule teens after school or to consider an occasional evening or weekend time and inform the teens of this availability.

Teens are a delightful patient population to serve, although initial encounters with them may be somewhat difficult. By establishing a relationship with a teen, the health care provider initiates a life-long comfort with the medical system.

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Molecular basis of pubertal abnormalities

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Puberty is a complex process, which involves the activation of hypothalamic function and maturation of the pituitary-gonadal axis. Disordered pubertal development, in the form of either delayed or precocious puberty, can be devastating and have long-term implications on the psychological and physical well-being of individuals. While the exact mechanisms regulating pubertal development are incompletely understood, advances in molecular genetics and technology have increased our comprehension dramatically over the past decade. Investigation of specific pubertal disorders with these new techniques has enabled us to identify a variety of genes involved in pubertal development. This article reviews the genetic causes of precocious and delayed puberty and discusses our current understanding of the molecular basis of these disorders.

Precocious puberty

Precocious puberty is defined as the onset of puberty before age 8 years in girls and age 9 to 9.5 years in boys, although the normative data used to set these limits has been challenged recently [1]. The etiology of precocious puberty is heterogeneous. Precocious puberty has been reported in several genetic disorders and in some females with chromosomal abnormalities (Table 1). Recently, investigators have started to use genetic association studies to identify susceptibility loci for

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Table 1
Genetic disorders associated with precocious puberty

Disorder	Gene or chromosome abnormality	Inheritance
McCune-Albright syndrome	GNAS1	Sporadic Somatic mosaicism
Williams syndrome	7q11.2 deletion	Sporadic
Neurofibromatosis type I	NF1	Autosomal-dominant

Abbreviations: NF1, Neurofibromatosis type I.

premature puberty. These studies have the potential to advance our understanding of the genetic basis of pubertal disorders but, to date, have not been reproducible.

McCune-Albright syndrome

McCune-Albright syndrome (MAS) is one cause of gonadotrophin-independent precocious puberty. Precocious puberty occurs in approximately 50% of females with MAS [2]. Symptoms may evolve rapidly during the first months of life, but they also may regress. Females may present with premature menses and males with testicular enlargement, spermatogenesis, and development of secondary sex characteristics [3]. In addition to precocious puberty, café au lait spots, recurrent ovarian cysts, and polyostotic dysplasia are common [2]. This is a highly variable disorder that also may include thyrotoxicis, pituitary gigantism, and Cushing syndrome. McCune-Albright is a sporadic disorder caused by gain of function mutations in the Guanine nucleotide-binding protein alpha subunit (GNAS)1 gene for the alpha subunit of the Gs protein [4,5].

The Gs protein is a ubiquitously expressed heterotrimeric molecule that is a member of a large family of G proteins involved in signal transduction. Mutations in GNAS1 result in the constitutive activation of adenyl cyclase, which stimulates the synthesis of cAMP from ATP within cells. Activation of Gs occurs through the GTPase cycle of the α-subunit. Missense mutations resulting in a substitution of histidine or cysteine for arginine at position 201 (Arg201) has been detected in various tissues from patients with MAS [3,5,6]. In two separate reports, glycine and leucine substitutions were reported in the same position. Located on chromosome 20q13.2-13.3, GNAS1 is a complex gene consisting of 13 exons with several alternatively spliced forms. The activating mutations are confined to exons 8 and 9 [6]. These mutations are confined to the somatic cells and most likely result from a postzygotic mutation. Hence, individuals with MAS are not at an increased risk for having affected offspring. It is presumed that germline mutations would not be viable [7]. Studies of cells obtained from the bone marrow involved in fibrous dysplasia from several patients have shown two different types of colonies: cells with two normal GNAS1 alleles, and cells with one activating mutation and one normal allele.

Several studies have shown that the distribution and level of mutations is variable [8]. The presence of specific features of MAS may be determined by the presence of a mutation in a particular type of tissue. For example, a mutation may be found in blood leukocytes but not normal skin. A GNAS1 mutation was

identified in a sample of fluid aspirated from a recurrent ovarian cyst in a 3-year-old individual with precocious puberty [9]. Clinical testing for mutations may be difficult to interpret because of mosaicism. Mutation analysis of DNA obtained from a blood sample may fail to detect a mutation in GNAS1 in patients with clinical findings consistent with the diagnosis of MAS. Therefore, a negative mutation study cannot exclude the diagnosis. Further, molecular studies cannot predict the distribution and the risk for developing skeletal lesions [8]. Activating mutations in GNAS1 have also been identified in individuals with isolated skeletal cases of fibrous dysplasia without MAS, suggesting that these represent a spectrum of features of the same disorder [10]. Several endocrine tumors, such as GH-secreting pituitary tumors, thyroid adenomas, Leydig cell tumors, pheochromocytomas, and ACTH-secreting pituitary tumors, also are associated with GNAS1 activating mutations [3,6].

Genetic syndromes, chromosomal abnormalities, and genes associated with precocious puberty

Central GnRH-dependent precocious puberty has been documented in several genetic disorders. Puberty may occur earlier in females and males with Williams syndrome, a disorder characterized by vascular anomalies, including supravalvular aortic stenosis, infantile hypercalcemia, a characteristic facies and behavior, and cognitive difficulties [11,12]. The majority of individuals with Williams syndrome have a deletion of chromosome 7q11.2. The incidence of precocious puberty is increased in individuals with neurofibromatosis type I (NF1). A longitudinal study of 89 children identified five patients with precocious puberty and normal pituitary and thyroid function; all five had central nervous system (CNS) lesions documented on imaging studies [13]. The incidence of precocious puberty was 2.4% in a retrospective study of 412 pediatric patients with NF1. The onset of puberty ranged from 5.2 to 7.5 years of age in girls and from 7.9 to 8.9 years of age in boys [14]. Two thirds of these patients also had optic pathway tumors. Two cases of precocious puberty have been reported in women with trisomy X (47,XXX) [15,16]. Two females with a supernumerary marker chromosome, an inv dup(15), had precocious puberty [17]. Individuals with this marker chromosome also may have seizures and mental retardation. Cytogenetic studies should be considered in the evaluation of a patient with precocious puberty and mental retardation. Early puberty in association with short stature and low birth weight also has been reported in a female with maternal uniparental disomy for chromosome 14. In this case, the patient inherited two copies of chromosome 14 from her mother, suggesting an imprinted gene on chromosome 14 is responsible for early onset of puberty, accelerated skeletal maturation, and intrauterine growth restriction [18].

LH receptor gene

Activating luteinizing hormone receptor (LHR) mutations have been identified in boys with gonadotropin-independent precocious puberty (testotoxicosis). A

variety of missense mutations have been identified in exon 11, which encodes the transmembrane domain. A defect in the transmembrane LH receptor triggers cAMP-dependent steroidogenesis. Starting in infancy, the testes secrete testosterone autonomously. Affected males experience rapid virilization, growth, and advanced bone age between 2 and 4 years of age. Testosterone levels are elevated, while LH levels are age-appropriate. Activating mutations have not been identified in females [19,20].

CYP polymorphisms

There is some evidence that genes responsible for ovarian hormone metabolism may affect pubertal development. The CYP3A4 gene is a cytochrome P450 enzyme responsible for the metabolism of testosterone. Kadlubar et al reported an association of the high-activity allele CYP3A4 * 1B with increased testosterone availability and early puberty in girls [21]. However, a more recent study evaluated this and other CYP polymorphisms with reported age at first menarche and found no significant association [22].

Delayed puberty

A variety of genetic alterations affecting the hypothalamic-pituitary-gonadal axis result in delayed puberty. Delayed puberty includes absence of the physical signs of puberty or failure to progress through puberty. Absence of thelarche by 13 years of age or menarche by 16 years of age in girls is considered delayed puberty. Boys with absence of testicular enlargement by 14 years of age are delayed. Genetic causes of delayed puberty include

Table 2
Genetic disorders associated with delayed puberty

Disorder	Genes or chromosomal abnormalities
Turner's syndrome	45,X or variant
	SHOX
Gonadal dysgenesis	SRY mutations
	DAX1 duplications
Adrenal hypoplasia	DAX1
Kallmann's syndrome	Kal1
Idiopathic hypogoanadotrophic hypogonadism	GnRH receptor
Prader-Willi syndrome	15q11-13 paternal deletions or maternal isodisomy
Bardet-Biedl syndrome	BBS1-6
Gonadotrophin abnormaliteis	FSHβ, LHβ, LH receptor, FSH receptor
CYP17 deficiency	CYP17
Aromatase deficiency	CYP19
Androgen Insensitivity syndrome	Androgen receptor
Hypogonadotrophic hypogonadism	Leptin, PROP1

Abbreviations: BBS, Bardet-Biedl syndrome; PROP, Prophet of PIT1.

chromosomal abnormalities (eg, 45,X) and single gene defects in a variety of genes listed in Table 2.

Turner's syndrome

In females, one of the leading causes of delayed puberty due to hypergonadotrophic hypogonadism is Turner's syndrome. The majority of females with Turner's syndrome do not develop secondary sex characteristics or have spontaneous menses. Pubertal development occurs in up to 30% of females with Turner's syndrome, and 2% to 5% of females with Turner's syndrome menstruate and may be fertile. However, these women are also more likely to experience delayed puberty and premature ovarian failure [23,24]. The incidence of Turner's syndrome is 1 in 1500 to 2500 female live births. Turner's syndrome is caused by complete (45,X karyotype) or partial absence of the X chromosome due to an isochromosome, a ring chromosome, or an intrachromosomal deletion. Isochromosomes of the X chromosome are missing the short arm and consist of two copies or a duplication of the long arm of the X chromosome. Ring X chromosomes are missing a variable portion of the end of both the short and long arm of the X chromosome. Over 25% of females with Turner's syndrome have two cell lines or mosaicism, such as 45,X/46,XX. Pubertal delay, cardiac and renal anomalies, and short stature are less likely in females with mosaicism. In some cases, a complete Y chromosome (45,X/46,XY) or partial Y chromosome may be present. With the exception of short stature, the clinical features are variable; therefore, Turner's syndrome may not be recognized until late childhood or during adolescence. The diagnosis should be suspected in a female with delayed puberty or pubertal arrest, absence of breast development by age 13 years, primary or secondary amenorrhea with an elevated FSH level, and unexplained short stature. Under these circumstances, a karyotype is recommended. Since mosaicism is not uncommon, an adequate number of cells (50–100) should be studied, and if a marker chromosome is present, fluorescence in situ hybridization (FISH) with a Y-chromosome probe is indicated. Females with Y chromosomal material have a 7% to 10% risk of developing gonadoblastoma; hence, gonadectomy is recommended [25]. Other manifestations in Turner's syndrome include webbed neck, neonatal edema of the hands and feet, coarctation of the aorta, renal anomalies, and skeletal anomalies, such as cubitus valgus, Madelung deformity, short neck, and short metacarpals.

Females with a single X chromosome undergo normal ovarian differentiation, but in the absence of two normal X chromosomes, the ovarian follicles degenerate, which suggests that two X chromosomes are necessary for maintenance of the ovary. Researchers have tried to identify the regions of the X chromosome and the genes that are critical for the maintenance of ovarian function by studying females with different deletions of the X chromosome [26,27]. These studies suggested that regions Xpter $\rightarrow$ p21 and Xq13 play a role in ovarian maintenance [27]. More recently, it has been proposed that gonadal function is related to the extent that chromosomes pair during meiosis [26]. Gonadal function

seems to correlate with the size of the unpaired region of the X chromosome. For example, ovarian function is maintained in females with small distal deletions of Xp and a small, unpaired region of the X chromosome. In contrast, females with an isochromosome of the long arm lack a short arm to pair with the normal X chromosome and have gonadal dysgenesis. It has been suggested that the chromosomal imbalance and lack of homologous chromosome pairing in meiosis in females with Turner's syndrome is also responsible for the developmental anomalies [26]. However, additional studies of patients with X-chromosome abnormalities are necessary before a conclusion is reached.

Comparison of the phenotype in females with varying deletions of the X chromosome also suggested that the locus for stature is located on the short arm of the X chromosome. Subsequent studies demonstrated that haploinsufficiency of the SHOX gene is responsible for the skeletal features and contributes to the short stature in females with Turner's syndrome [28,29]. SHOX (short stature homeobox-containing gene) consists of 7 exons and maps to the distal psuedoautosomal region on the short arm of the X chromosome (Xp22.3). It is highly expressed in osteogenic tissue and the first and second pharyngeal pouches. SHOX deletions and mutations also have been shown to cause Leri-Weill dyschondrosteosis, an inherited skeletal dysplasia characterized by short stature and similar skeletal findings to Turner's syndrome [30,31]. However, comparisons of these two populations suggest that haploinsufficiency for SHOX is responsible for only two thirds of the height deficiency in Turner's syndrome and that other loci contribute to short stature [32].

Lymphedema is a variable feature of Turner's syndrome and may spontaneously resolve in the fetus or in childhood. The putative gene responsible for lymphedema also seems to reside on the short arm of the X chromosome (Xp). Analysis of individuals with Xp deletions suggests that the gene is in distal Xp11, a region that escapes inactivation, and has a homologous gene on Yp [26]. Ogata et al proposed that the putative lymphogenic gene may be responsible for the cardiac and renal anomalies [26]. Alternatively, a second lymphogenic gene on the long arm or the chromosomal imbalance is responsible for the development of these anomalies.

Gonadal dysgenesis

Hypergonadotrophic hypogonadism and delayed puberty may occur with 46,XX and 46,XY gonadal dysgenesis. Like Turner's syndrome, the females have normal Mullerian derivatives and streak gonads. A case report of two affected sisters with 46,XX and 46,XY karyotypes suggests that this may be an autosomal-recessive disorder [33]. In complete 46,XY gonadal dysgenesis, ambiguous genitalia in combination with delayed puberty may be observed. sex-determining region Y (SRY) gene mutations have been identified in approximately 15% of 46,XY individuals with gonadal dysgenesis [34]. SRY is the testes-determining gene located on the distal short arm of the Y chromosome. Duplications of dosage-sensitive sex reversal-adrenal hypoplasia congenita critical region on the

X chromosome, gene-1 (DAX1) also may result in gonadal dysgenesis and 46,XY sex reversal [35].

Adrenal hypoplasia and DAX1

Adrenal hypoplasia, an X-linked recessive disease associated with delayed puberty in males, is caused by mutations in DAX1. Affected boys experience life-threatening adrenal failure in infancy and require mineralcorticoid and glucocorticoid replacement. Surviving children fail to mature sexually at puberty due to hypogonadotropic hypogonadism. DAX1 maps to the short arm of the X chromosome and encodes a protein called DAX-1, which is a nuclear hormone receptor that seems to mediate gonadotropin secretion at the hypothalamic and pituitary level. DAX1 is important for normal adrenal gland development and sexual maturation. It plays a critical role in testicular development and spermatogenesis, and its over-expression results in feminization of XY individuals [35]. More than 60 different mutations in DAX1 have been reported in males with adrenal hypoplasia. While the clinical presentation is variable—ranging from minimal adrenal dysfunction with delayed puberty to severe adrenal insufficiency and undescended testes—the severity of the disease does not seem to correlate with the type of mutation [24,36,37]. Female carriers of DAX1 mutations may display pubertal delay [38]. This suggests that epigenetic factors may be involved in phenotypic expression [36]. DAX1 mutations are not a common cause of constitutional pubertal delay in patients without adrenal insufficiency [39].

Idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome

Isolated GnRH deficiency results in a suppressed pituitary-gonadal axis, causing delayed puberty and infertility. GnRH-induced LH pulsations are absent, pituitary-gonadal function normalizes with GnRH replacement, and cerebral imaging is unremarkable. The clinical presentation is extremely variable, ranging from complete failure of sexual maturation with cryptorchidism, microphallus, and pubertal failure, to reproductive failure after the completion of puberty. Autosomal-dominant, autosomal-recessive, and X-linked forms of inheritance have been described. Several gene mutations have been associated with this disorder, accounting for only 20% of idiopathic hypogonadotropic hypogonadism (IHH), while the majority of IHH remain unexplained [40–45]. Kallmann's syndrome has been distinguished from IHH only by the presence of abnormal olfaction. It has been observed that Kallmann's and IHH may exist within the same family. It is unclear whether Kallmann's syndrome and IHH represent two distinct etiologic entities or whether they reflect phenotypic variation within one disease process [46,47].

KAL gene

The gene for the X-linked form of Kallmann's syndrome has been identified on the pseudo-autosomal region of the X chromosome (Xp). The KAL gene

encodes a protein, anosmin, which seems to play a role in the migration of GnRH neurons from the olfactory placode to the hypothalamus. Absent or defective anosmin results in abnormal hypothalamic function [48,49]. While all patients experience hypogonadotropic hypogonadism and anosmia, other abnormalities may coexist. Movement disorders, visual problems, midline facial defects, and renal agenesis can be explained by KAL gene expression in the olfactory bulb, oculomotor nucleus, cerebellum, midface, and metanephros [50]. Deletions, missense, and nonsense mutations have been reported in the KAL gene [44,51–54]. The phenotypic heterogeneity in this disease is remarkable and does not correlate with a specific genotype [44].

Gonadotrophin-releasing hormone receptor (GNRHR) gene

The first autosomal-recessive form of IHH involved mutations in the GnRH receptor (GNRHR) gene. This receptor is a G protein–coupled receptor with seven transmembrane domains. Mutations in this gene were found in 2.2% of IHH patients. In this gene, approximately 10 different inactivating mutations have been identified that cause impaired receptor signal transduction in the pituitary. Most affected patients were found to be compound heterozygotes for missense mutations [55]. As in other forms of IHH, there is a broad phenotypic spectrum associated with GNRHR mutations, ranging from incomplete sexual maturation to complete pubertal failure. There is also a variable response to GnRH therapy, which is thought to relate to the degree of receptor dysfunction [36,43,55].

Other genetic disorders associated with delayed puberty

Delayed puberty due to hypogonadotrophic hypogonadism is also seen in Prader-Willi syndrome in association with short stature, hypotonia, and obesity. Prader-Willi syndrome is caused by either paternal deletions of chromosome 15q11-13 or maternal disomy of chromosome 15 (eg, two maternal copies, no paternal copy). Hypogonadism in males, primary gonadal failure, hypogonadotrophic hypogonadism, and genital abnormalities in females are common in Bardet-Biedl (formerly referred to as Laurence-Moon-Biedl) syndrome. Other features include retinal dystrophy, obesity, polydactyly, cognitive impairment, and renal dysgenesis. Bardet-Biedl syndrome (BBS) is a rare, complex, and heterogeneous disorder that seems to be autosomal-recessive; however, recent studies suggest more than one gene or at least three alleles are involved in the pathogenesis of this disorder. At least six genes have been linked to BBS, and homozygous or compound heterozygous mutations in three of the genes have been identified in individuals with BBS [56].

Gonadotrophins and their receptors

Several mutations have been identified in the genes that encode the gonadotrophins and their receptors, resulting in delayed or absent puberty.

FSHβ-subunit gene

The necessity of FSH for normal female pubertal development is highlighted by the findings that women with FSH mutations undergo abnormal sexual maturation. Affected women demonstrate delayed puberty with absent thelarche, primary amenorrhea, and infertility. Affected males suffer from azoospermia, but puberty may be normal. FSH seems to be necessary for normal spermatogenesis. Inheritance is autosomal-recessive. Recently, mutations in the gene coding for the β subunit of FSH have been identified in both men and women. The most common mutation is a 2 bp deletion in codon 61, resulting in the formation of a truncated FSH β-protein [19,57–60].

LHβ-subunit gene

One male with delayed puberty and arrest of spermatogenesis has been reported with a missense mutation in the gene coding for the β subunit for LH (A–G on codon 54). This mutation resulted in inactivation of LH, causing low serum testosterone. This case emphasizes the importance of LH in male pubertal maturation and fertility [19,61]. No mutations in this gene have been documented in females.

LH receptor gene

The LH receptor is a G protein–coupled receptor, which binds both LH and hCG. Inactivating LH receptor mutations result in pseudohermaphroditism and delayed puberty in males [62,63]. In a 46,XY individual, homozygosity for a mutation in this gene typically results in female external genitalia, owing to absent testosterone-induced sexual differentiation and an absent uterus resembling complete androgen insensitivity. However, unlike androgen insensitivity, testosterone levels are low and pubertal feminization does not occur because testosterone is not available for peripheral aromatization. The degree of receptor inactivation dictates the phenotype. Females with inactivating LH receptor mutations undergo normal puberty but experience anovulatory amenorrhea [64]. Hence, it seems that LH action is necessary for normal male, but not female, pubertal maturation. In females, LH is necessary for ovulation and luteinization of follicles [65].

FSH receptor gene

The first inactivating FSH receptor (FSHR) mutation causing delayed puberty was identified in a Finnish population [66]. A missense mutation (Ala189Val) causes a structural change in the FSH receptor blocking signal transduction. Females homozygous for this mutation have hypergonadotropic hypogonadism with primary amenorrhea and variable breast development. Partial loss of function mutations have been identified that result in normal development but secondary amenorrhea [67]. It seems that the severity depends on the degree to which receptors are impaired. Males with FSHR mutations develop normally except for demonstrating a wide variation of abnormal semen parameters [68,69].

Abnormalities in steroidogenesis

CYP17 deficiency

The CYP17 gene encodes a cytochrome P450 enzyme that has both 17-hydroxylase and 17-20 desmolase activity. This enzyme plays a critical role in the production of progestins, androgens, estrogens, and cortisol. A CYP17 mutation and subsequent enzyme deficiency result in a deficiency of these hormones and an excess of mineralcorticoids. CYP17 deficiency is an autosomal-recessive condition, and many different mutations have been identified. Pubertal failure due to hypergonadotropic hypogonadism is found in affected females and males [35].

Aromatase deficiency

The CYP19 gene seems to play an important role in pubertal development. It codes for the enzyme aromatase, which converts androgens to estrogens in various tissues throughout the body. Various mutations in this gene, resulting in either absent or abnormal aromatase, have been identified [70–72]. Aromatase deficiency is an autosomal-recessive disorder. In affected females, ambiguous genitalia are present at birth, pubertal failure with hypergonadotropic hypogonadism occurs, and the ovaries are multicystic. Females are anovulatory, and it is speculated that mild forms of this disorder may result in polycystic ovary syndrome. Virilization with elevated circulating androgens also has been documented in females with this disorder [8,16,73,74]. Males seem to have normal pubertal development but experience continued linear growth and osteoporosis from incomplete epiphyseal closure. These observations indicate that while estrogen is necessary for pubertal development in girls but not in boys, estrogen plays an important role in epiphyseal closure in boys [72,75]. The effect of this mutation on fertility is unclear. In males, a knockout mouse model demonstrates abnormal spermatogenesis and impaired fertility, but this has not been definitively seen in humans [76].

Androgen insensitivity

Incomplete puberty with delayed menarche may result from androgen insensitivity syndrome (AIS). If undetected in infancy or childhood, females typically present in adolescence with primary amenorrhea, normal breast development, and scanty pubic hair. The uterus is absent, and the vagina ends blindly and may be shortened. In most cases, the Wolffian duct derivatives are absent, although rudimentary segments of both Mullerian and Wolffian ducts may be found. The gonads or testes may be found in the inguinal region. Partial forms of androgen insensitivity exist and may cause ambiguous genitalia. Individuals with AIS have a 46,XY karyotype. Androgen insensitivity is caused by mutations in the androgen receptor (AR) gene on the proximal long arm of the X chromosome (Xq11). Over 300 mutations have been reported, including single nucleotide substitutions resulting in amino acid substitutions or premature stop codons; nucleotide deletions or insertions leading to frameshifts and premature stop codons; partial or complete

gene deletions; and intronic mutations that affect splicing [77]. An androgen receptor gene mutations database is available at www.mcgill.ca/androgendb.

Familial cases of AIS are not uncommon. The mothers of females with AIS may be carriers and should receive genetic counseling or testing to assess carrier status if a mutation is identified in the patient. Female carriers have a 50% risk of transmitting the mutation to their male offspring and a 25% risk of having an affected child. Molecular diagnostic testing is available, although the sensitivity of testing is greater for complete forms of androgen insensitivity syndrome (CAIS). Ahmed et al were able to identify mutations in only 28% of the individuals with partial AIS (PAIS) compared with 83% with CAIS [78]. Following identification of a mutation in an affected individual, carrier testing is possible, and if an individual is found to be a carrier, prenatal diagnostic testing can be performed. Phenotypic variability has not been observed in CAIS. In contrast, approximately one third of the familial cases of PAIS exhibit variability [79]. It can be difficult to predict the outcome based on the specific mutation or the family history.

The gene contains eight exons and consists of a DNA-binding domain, a bipartite nuclear localization signal, a C-terminal androgen-binding domain, and an amino-terminal transregulation modulatory portion containing two trinucleotide repeats of variable length. Expansion of the polyglutamine (CAG) tract is associated with Kennedy syndrome or spinal bulbar motor neuronopathy [80]. In general, mutations in exon 1 cause CAIS, although several cases of PAIS have been reported [81]. Most mutations occur in exons 2 through 8, including the DNA and androgen-binding domains. Mutations in the DNA binding domain (exons 2 and 3) may cause either CAIS or PAIS [82]. Variable expression has been observed in AIS in association with specific mutations or as a result of somatic mosaicism [81–83]. Many co-regulatory proteins that interact with the AR may also influence the clinical phenotype.

Genes involved in pubertal development

In addition to the genetic and chromosomal disorders described above, there have been several new developments in our understanding of the genes that are critical to normal pubertal development.

Leptin

There is substantial evidence that leptin is an important factor regulating pubertal development and reproduction [84]. It is recognized that normal puberty requires the existence of a critical fat mass. Secreted by adipose tissue, leptin is a hormone that relays information about nutritional status to the brain and other tissues. It is encoded by the obesity (ob) gene, and receptors have been identified at all levels of the hypothalamic-pituitary-gonadal axis. High leptin levels in the ovary interfere with steroidogenesis and normal ovulation, while in the testes leptin inhibits testosterone production [85]. It seems that leptin has opposing effects at

different levels, stimulating the hypothalamic-pituitary axis centrally and inhibiting gonadal function peripherally. This may explain why either an excess or deficiency of this hormone is associated with reproductive dysfunction.

A rise in leptin may be the earliest signal activating the HPG axis in puberty. Evidence in the mouse model has shown that either leptin administration in normal mice or an over-expression of endogenous leptin is associated with early onset puberty [86–88]. In humans, increased leptin levels have been associated with earlier menarche [89]. The discovery of inactivating mutations in the leptin gene or receptor associated with hypogonadotropic hypogonadism lends further support to the theory that leptin is necessary for normal puberty. These patients were notably obese and hyperinsulinemic, in addition to having pubertal delay [90,91]. Importantly, recombinant leptin treatment in a patient with a mutation in the leptin gene resulted in weight loss and increased gonadotropin levels [92].

GnRH gene

GnRH is thought to be crucial for normal pubertal development. However, while no specific genetic mutation in the GnRH gene has been identified in the human, a GnRH gene deletion has been found to be associated with IHH in the hypogonadal (hpg) mouse [93]. This finding supports the role of GnRH in puberty.

PROP1 gene

Prophet of PIT1 (PROP1), a transcription factor essential for the normal development of the anterior pituitary, has been identified on the long arm of chromosome 5. Activation of the PROP1 gene seems to be necessary during embryonic organogenesis, and suppression is required after birth for normal growth and differentiation of the pituitary gland [94]. Mutations in the PROP1 gene result in a hypocellular pituitary with decreased function in several cell lines [95]. More than 11 inactivating mutations have been identified in the PROP1 gene associated with combined pituitary hormone deficiency (CPHD), the most common being a two-base pair deletion in exon 2 (301–201delAG) [63,96,97]. Affected patients are homozygous or compound heterozygotes for inactivating PROP1 mutations and experience CPHD of growth hormone, thyroid stimulating hormone, prolactin, and gonadotrophins. The deficit in gonadotropins leads to pubertal failure. There is considerable phenotypic variability unrelated to the type of mutation; thus, the age of onset and severity of CPHD is unpredictable [98].

Summary

The causes of abnormal pubertal development are numerous. Recent molecular investigation has increased our understanding of the genetic basis of pubertal disorders. Investigators have identified some of the genes that are critical for

normal puberty and have begun to elucidate the genes and pathogenesis of genetic disorders associated with abnormal pubertal development. Identification of specific chromosomal abnormalities and gene mutations allows for diagnostic testing and enables the clinician to provide accurate counseling of the recurrence risk for relatives. In the future, knowledge of the genetic basis of these disorders will facilitate the development of novel therapies and approaches to the fertility assessment and treatment of individuals with pubertal disorders. Although great strides have been made in identifying these genes, questions remain. Why do some genetic mutations affect puberty differentially in males and females? What is the long-term impact in terms of future fertility, and what is the risk to the offspring of such patients? Further research is needed to address these issues and to identify additional genetic loci involved in pubertal development.

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Normal onset of puberty
Have definitions of onset changed?

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Puberty is the sequence of events in an individual's life that culminates in physical, sexual, and emotional maturation. This sequence of events is caused by the maturation of the hypothalamic-pituitary-gonadal (HPG) axis.

Maturation begins with a significant rise in gonadotropin secretion during fetal life that persists during infancy and goes into a quiescent phase during childhood. The onset of puberty results from the episodic release of luteinizing hormone (LH) and follicular stimulating hormone (FSH). This release reflects the intermittent release of GnRH from the hypothalamus in greater quantities and more frequent pulses.

The physiology of puberty

The fetal, infancy, and childhood period

By 10 weeks of gestation, GnRH is present in the hypothalamus and functionally active after 20 weeks of gestational age [1], and the pituitary responds to GnRH stimulation by secreting LH and FSH. GnRH and gonadal secretion progressively increase and stimulate gonadal maturation and hormone production. At birth, the levels of gonadotropins and sex steroid hormones are high, but they decline after a few days. In response to the decline in circulating sex steroids originating from the placenta, the gonadotropin levels start to rise again during the first week of life. During the next several weeks, levels of gonadotropins and

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gonadal hormones continue to be higher than the levels in older children. This suggests that the gonads are responsive to stimulation and are fully functional. Gonadotropins and sex steroids peak at 2 to 3 months of age, after which they drop to low levels for many years. The fall in gonadotropin levels occurs not only because of an adjustment in the negative feedback mechanism but also because of probable Central Nervous System (CNS) control of gonadotropin secretion (this fall in gonadotropin levels also is seen in agonadal children). Even though gonadotropin levels are lowest during mid-childhood, measurable amounts of gonadotropin are present, indicating some amount of episodic release [2]. Hence, a small amount of sex steroids, including estrogen, may be present in some children [3].

Puberty

Gonadotropin-releasing hormone and gonadotropins

The HPG axis is active in fetal life, and the pituitary and gonads are ready to respond with the appropriate stimulation by GnRH and the gonadotropins, respectively. Control is at the level of GnRH stimulation or a higher CNS loci. Preceding the onset of and during puberty, the mean levels of the gonadotropins rise, reflecting the increased episodic release of gonadotropins in response to pulsatile GnRH secretion. Due to this alteration in GnRH secretion, gonadotropin secretion is enhanced. A low level of gonadotropin secretion, with a low frequency and amplitude that increase during sleep, is present in prepubertal children [1–5]. As pubertal maturation progresses, the frequency and amplitude of these pulses increase. During early puberty, these pulses are seen more frequently during sleep than in the wakeful state. These change are more dramatic for LH than for FSH, with the rise in LH being greater than FSH during puberty [6]. In adults, the episodic rise in LH occurs every 90 minutes and lasts for approximately 20 minutes. The episodic release of FSH occurs less dramatically and is greater during sleep. These episodic phenomena are produced by the maturation of the CNS-stimulating influences that affect the GnRH pulse generator. Thus, pubertal change of the hypothalamus and the pituitary involves the increase of GnRH, LH, and FSH pulsatile secretion rather than the onset of secretion. The secretion of GnRH (12–18 times every 24 hours) is regulated by a region in the arcuate nucleus of the medial basal hypothalamus. At the onset of puberty, GnRH stimulation exerts a priming effect on the pituitary and causes a progressive increase in gonadotropins. This increased responsiveness also is accompanied by an increase in GnRH receptors in the pituitary.

Adult levels of LH and FSH are regulated by gonadal hormone secretion through a negative feedback mechanism and in the middle of the menstrual cycle through a positive feedback mechanism.

Sex steroids

The rise of gonadotropins and of sex steroids from the gonads and the adrenal cortex occurs before the onset of puberty. The increase in adrenal androgen pro-

duction, or adrenarche, is responsible for the onset of pubic hair growth (pubarche). The increase in gonadal sex steroid production is known as gonadarche.

Adrenarche. The adrenal androgens may be the first hormones to be elevated in puberty. The appearance of pubic and axillary hair, acne, and body odor may be the result of adrenal androgen production since these findings can occur without the presence of gonadal steroids and before any other signs of pubertal development.

The cause of adrenarche is not known. Elevated gonadotropin secretion does not cause an increase in adrenocorticotropic (ACTH) secretion. ACTH levels also do not increase at adrenarche; however, the response of the adrenal steroids to ACTH changes. The androgens are more sensitive to ACTH stimulation than the other adrenal steroids, and this response parallels the development of the adrenal zona reticularis.

Gonadarche. Gonadarche occurs due to the elevation in circulating gonadal steroids, especially estrogens in girls, in response to gonadotropin stimulation.

Other factors influencing the onset of puberty

Leptin, a hormone derived from adipose tissue, plays a role in body composition. It is hypothesized that body mass and composition regulate the onset of puberty. Because leptin levels rise during puberty, there is considerable interest in the role of leptin in the onset of puberty [7,8].

Activin and Follistatin are two other hormones that regulate follicular maturation and atresia. Although the levels of these hormones do not change during puberty, they do change during adulthood [9].

Other factors, such as excessive exercise, inadequate nutrition, and psychiatric illnesses (eg, anorexia nervosa), are associated with hypogonadotropic states that alter the onset of puberty.

Genetic regulation of the timing of puberty is seen in a correlation between the ages at which a mother and her offspring attain pubertal milestones [10]. Studies of twins demonstrate that pubertal milestones display more similarity between monozygotic twins than dizygotic twins [11–14].

Patterns of onset: have definitions changed?

The pubertal sequence of events follows a certain pattern. Usually the first sign is accelerated growth, followed by breast development, adrenarche, and menarche. This sequence of events on average requires a period of 4.5 years (range 1.5–6 years). Pubertal development has started occurring earlier, partly due to better socioeconomic conditions, especially nutritional status. Racial differences do exist in the onset and progression of puberty, with secondary sexual characteristics developing earlier in African-American girls than in white girls.

Previously, it was accepted that normal puberty in girls does not begin before 8 years of age. In 1997, the American Academy of Pediatrics published a cross-

Table 1
Cross-sectional study of pubertal development in black and white American girls

Pubertal event	Black American girls	White American girls
Breast or pubic hair		
Age 7 y	27.2%	6.7%
Age 8 y	48.3%	14.7%
Menarche		
Age 11 y	27.9%	13.4%
Age 12 y	62.1%	35.2%
Thelarche (mean age)	8.87 y	9.96 y
Adrenarche (mean age)	8.78 y	10.51 y
Menarche (mean age)	12.16 y	12.88 y

Abbreviations: y, years.

sectional study of pubertal development in American girls who were seen in pediatric office practices. This large multicenter study of 17,077 girls consisted of 90.4% white Americans and 9.6% black Americans [10]. Table 1 contains the important findings of the study.

The data revealed that the prevalence of breast or pubic hair before 8 years of age was 27% in black girls and 7% in white girls. By 9 years of age, 48% of black girls and 15% of white girls showed some sign of pubertal development. The mean age of menarche—12.2 years in black girls and 12.9 years in white girls—did not differ significantly from other reports. This study suggests that even though puberty is occurring earlier than previously thought, menarche is not occurring earlier and puberty is not completed earlier. In girls who showed an earlier onset of puberty, growth may be taking place at a slower pace or initial breast development may not be associated with the onset of real puberty. Maybe this earlier onset can be attributed to a different subset of the population, which influenced the overall data. A contributing factor could be that these data are derived from office practices instead of a random sampling of the population.

As a result of this study, new guidelines were recommended to redefine precocious puberty in girls from the onset of breast development before 8 years of age to the onset of breast or pubic hair before 7 years of age in white girls and 6 years of age in black girls [11]. We should be cautious in redefining the onset of puberty based on one study. Precocious puberty can be the result of a serious disorder, and diagnosis involves more criteria than age. Puberty that progresses so rapidly that growth and development are clearly excessive for age, should be evaluated and therapy to suppress pubertal development should be considered.

Stages of pubertal development

In general, the first sign of puberty is an acceleration of growth followed by breast budding. Breast development follows a series of events, with adrenarche usually following thelarche by 2 years. In some cases the sequence may be reversed, with pubic hair being the first sign of puberty in approximately 20% of

girls. Menarche is a late event that occurs during deceleration of the growth phase. About 90% of menstrual cycles may not be ovulatory until 6 to 7 years after menarche. Table 2 outlines the mean developmental pattern of puberty in girls [10–18].

The following sections describe the stages of pubertal development:

Growth and skeletal maturation
Thelarche (breast development)
Adrenarche
Menarche

Growth and skeletal maturation

In girls, the growth spurt occurs early compared with boys and occasionally precedes thelarche. Peak growth occurs when breast development is between Tanner stages 2 and 3. Sex steroids, especially estrogen, play an important role in the skeletal growth that occurs during puberty in both women and men. Estrogen is a potent stimulator of bone growth, and it is necessary for the closure of the epiphysis. Individuals with aromatase deficiency or estrogen receptor mutations continue to grow into adulthood and become very tall [14–21]. Estrogen also plays a critical role in the accumulation of bone mass, with peak bone mass attained late in puberty. Besides estrogen, the presence of growth hormone and insulin-like growth factor-I are necessary for growth [22].

Thelarche

The average of onset of breast budding is approximately 10 years of age and reflects the progressive increase in estrogen stimulation and production. Breast

Table 2
Sequence of pubertal events in girls

Pubertal event	Mean age
Breast development (Tanner stage 2)	10.0–10.5
Pubic hair growth (Tanner stage 2)	10.3–10.8
Maximum growth rate	11.2–11.7
Maximum rate of weight gain	11.7–12.2
Breast development (Tanner stage 3)	11.3–11.8
Pubic hair growth (Tanner stage 3)	11.4–11.9
Onset of axillary hair	12.3–12.8
Menarche	12.6–13.1
Breast development (Tanner stage 4)	12.5–13.0
Pubic hair growth (Tanner stage 4)	12.5–13.0
Regular menses	13.7–14.2
Breast development (Tanner stage 5)	14.0–14.5
Pubic hair growth (Tanner stage 5)	14.0–14.5

development follows a well-recognized sequence of events characterized by the following Tanner stages [23]:

Absence of breast bud
Presence of breast bud only
Enlargement of entire breast mound
Secondary areolar mound on top of the primary mound
Adult mature breast contour, secondary mound no longer evident

Adrenarche

The appearance of pubic hair is the next change seen in puberty. The texture of the pubic hair is longer and coarser than the body hair of childhood. Pubic hair development, which reflects increased androgen production, is characterized by the following Tanner stages [23].

Nonsexual, general body hair
Long, coarse, pigmented hair, usually appearing along the labia majora
Greater concentration of coarse, long hair extending to the mons pubis
Abundance of coarse, dark pubic hair on the mons and labia
Pubic hair present in an adult pattern, an inverted triangle extending to the thighs

Menarche

The mean interval between breast budding and the onset of menses is approximately 2 years. This may vary: the earlier the thelarche, the longer until menarche [24]. Menarche depends on hormonal levels during early puberty, with higher levels leading to an earlier onset [25]. Menarche most commonly occurs during stage 3 or 4 of breast development.

The median age of the onset of menses in American girls is 12.8 years (range of 9.1–17.7 years) [13,26]. The menses following menarche are usually anovulatory, with 25% to 50% of girls anovulatory 4 years after menarche [27,28].

Menarche occurs after the growth spurt has passed. Slower growth (on average, 6 cm or 2.4 in) occurs after menarche.

Variations

Variation in the duration of pubertal development represents diversity in the rate of maturation and attainment of full reproductive function. Complete breast development can take 3 years or longer, with 3 to 4 years required for pubic hair development. Prepubertal development of sexual hair as an isolated event is known as premature pubarche, and isolated breast development is known as premature thelarche. Both can represent the onset of precocious puberty; however, once precocious puberty is ruled out, these events by themselves are innocuous.

Summary

Puberty is the sequence of events that culminates in the ability to procreate. It is widely accepted that the onset of puberty in girls occurs on average at 8 years of age and that onset prior to 8 years of age is precocious puberty. As a result of the cross-sectional study by the American Association of Pediatrics, a movement exists to change the age limit of the onset of puberty to 6 years of age in black girls and 7 years of age in white girls. We should be cautious in adhering to strict age limits when diagnosing precocious puberty. Also the rapidity and progression of puberty should be evaluated, and if appropriate, therapy to suppress pubertal development considered.

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OBSTETRICS AND GYNECOLOGY CLINICS of North America

Contemporary issues in primary amenorrhea

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In 1981, a study of 252 patients who presented with pubertal aberrancy was published [1]. In 1986, the study was expanded to 326 patients, from which 266 (82%) were identified with primary amenorrhea [2]. A retrospective description of a large sample from a wide-based referral population, this study likely represents such abnormalities present in the general population.

Many clinicians do not like to consider primary and secondary amenorrhea separately, because a number of causes of secondary amenorrhea also could cause primary amenorrhea. However, unlike secondary amenorrhea, primary amenorrhea comprises patients who can never have spontaneous menses or spontaneous reproduction. These patients present challenges to physicians who counsel young, recently diagnosed adolescents about their inability to conceive. Similarly, they present challenges to reproductive endocrinologists who design fertility treatment.

During the 20 years since the original publication, little has changed in medicine that would alter the numeric breakdown of these disorders at presentation. However, reproductive medicine has been affected by the advent of two revolutions: molecular medicine and assisted reproductive technologies (ART). As a result, contemporary thought about these disorders is very different from the basic phenotypic knowledge present in 1981.

Understanding the molecular basis of many of these disorders has uncovered the mystery of some: follicle-stimulating hormone (FSH) receptor mutations in ovarian resistance (Savage syndrome); mutations of the DNA-binding domain in patients with androgen insensitivity syndrome (AIS) who had normal androgen binding assays; GnRH receptor mutations in patients with idiopathic hypogonadotropic hypogonadism who never responded to pulsatile GnRH therapy; and SRY gene mutations in patients with Swyer syndrome.

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In recent years, pregnancies have occurred for the first time for a number of the patients in the original study who were thought to have an absolute barrier to reproduction. For some, the use of donor oocytes (46,XX and 46,XY gonadal dysgenesis) or gestational carriers (women with congenital absence of the uterus and vagina [CAUV]) has provided an alternative to adoption. For Turner's syndrome patients, this alternative is accompanied by significant risk of maternal death. We have gained insight into the genetics of disorders for which reproduction was not previously possible (eg, the delivery of infants by surrogacy for patients with CAUV).

Our understanding about the disorders presenting with primary amenorrhea has changed dramatically in the past 20 years. We can diagnose some disorders more accurately, provide more effective counseling, and in some cases, offer real options for becoming biological parents. Using data from the original pubertal study to understand the numeric frequency of primary amenorrhea disorders, we provide contemporary thoughts about these disorders in this article.

Definition of primary amenorrhea

Traditionally, primary amenorrhea is defined as delayed menarche by 14 years of age in the absence of secondary sexual characteristics or absence of menses by 16 years of age in the presence of normal growth and secondary sexual characteristics.

Elsewhere in this issue, evidence is presented that puberty may be occurring earlier than previously thought. Based on this evidence, a revision of the definitions of precocious puberty has been proposed. Given that no such consideration for changing the definition of delayed puberty and, thus, primary amenorrhea has been proposed, the traditional definitions might not entirely reflect contemporary standards.

Furthermore, rather than delay evaluation until these young women meet the strict definitions of primary amenorrhea, it is suggested that all adolescents be followed annually through the pubertal process to identify abnormalities as they become apparent. It is preferable to initiate a partial evaluation when abnormalities first become apparent instead of waiting until these young women differ significantly from their peers [3]. Normal adolescence can be a difficult time in any individual's life. When significant deviations in secondary sexual development occur, prompt evaluation, treatment, and counseling should immediately follow rather than waiting until the adolescent meets the strict definition of primary or secondary amenorrhea.

Classification of primary amenorrhea

Several approaches have been used to classify the causes of primary amenorrhea. One approach applies the same classification to both primary and secondary

amenorrhea (delayed puberty), that is, classification according to presence or absence of gonadal function in combination with physical examination. Hypogonadism refers to gonads that are not functioning (ie, associated with a hypoestrogenic state), and eugonadism refers to gonads that maintain normal steroidogenesis (ie, associated with a well-estrogenized state). Tables 1 and 2 present a causal breakdown.

Table 1
Causal breakdown of 266 patients with primary amenorrhea

Cause of primary amenorrhea	Number	Percentage
Hypergonadotropic hypogonadism		
Abnormal sex chromosomes		
Turner's syndrome	79	29.7%
Normal sex chromosomes		
46,XX	41	15.4%
46,XY	9	3.4%
Total	129	48.5%
Hypogonadotropic hypogonadism		
Congenital abnormalities		
Isolated GnRH deficiency	22	8.3%
Forms of hypopituitarism	6	2.3%
Congenital CNS defects	2	0.8%
Constitutional delay	16	6.0%
Acquired lesions		
Endocrine		
CAH	2	0.8%
Cushing's syndrome	1	0.4%
Pseudohypo-parathyroidism	1	0.4%
Hyperprolactinemia 5 1.9%		
Tumor		
Unclassified pituitary adenoma	2	0.8%
Craniopharyngioma	3	1.1%
Unclassified malignant tumor	1	0.4%
Systemic illness	7	2.6%
Eating disorders	6	2.3%
Total	74	27.8%
Eugonadism		
Anatomic		
CAUV	43	16.2%
Cervical atresia	1	0.4%
Intersex disorders		
Androgen insensitivity	4	1.5%
17-ketoreductase deficiency	1	0.4%
Inappropriate feedback	14	5.3%
Total	63	23.7%

Percentages rounded to the nearest tenth.
Abbreviations: CAUV, congenital absence of the uterus and vagina; CNS, central nervous system; CAH, congenital adrenal hyperplasia.
Data from Reindollar RH, Tho SPT, McDonough PG. Delayed puberty: an updated study of 326 patients. Transactions of the American Gynecological and Obstetrical Society 1989;8:146–62.

Table 2
Causes of primary amenorrhea

Hypogonadism
Hypergonadotropic hypogonadism
Abnormal sex chromosomes
Turner's syndrome
Normal sex chromosomes
46,XX gonadal dysgenesis
46,XY gonadal dysgenesis
Pseudo-ovarian failure
Hypogonadotropic hypogonadism
Congenital abnormalities
GnRH deficiency
Gene mutations
Constitutional delay
Acquired abnormalities
Endocrine disorders
Pituitary tumors
Systemic disorders
Eugonadism
Anatomic abnormalities
CAUV
Imperforate hymen
Transverse vaginal septum
Intersex disorders
Androgen insensitivity
PCOS

Abbreviations: CAUV, congenital absence of the uterus and vagina; PCOS, polycystic ovarian syndrome.

At the initial consultation, determining the patient's estrogen status either by the absence (hypoestrogenic) or presence (well-estrogenized) of breast development or by the absence (hypoestrogenic) of superficial cells on vaginal cytology direct the physician to potential causes of primary amenorrhea (see Table 1). A pelvic examination further narrows these causes by determining the presence or absence of a normal mullerian system.

Hypogonadism

Hypergonadotropic hypogonadism

In young women presenting with primary amenorrhea, the single most common cause is primary ovarian failure due to gonadal dysgenesis [2]. These patients have significantly elevated gonadotropin levels due to ovarian failure. The largest number of patients with ovarian failure has Turner's syndrome, followed numerically by 46,XX gonadal dysgenesis, and, rarely, 46,XY gonadal dysgenesis (see Table 2).

Turner's syndrome

Turner's syndrome women represent the largest number of patients with primary ovarian failure (see Table 1) and have the classic 45,X karyotype associated with Turner's syndrome (30% of patients) or mosaic forms of Turner's syndrome [1]. Patients with mosaic forms of Turner's syndrome usually have a 45,X cell line associated with another cell line, such as 46,XX or 46,XY [4]. Structural abnormalities of the X chromosome, such as isochromosome for the long arm of X (ie, i[Xq]), may occur as single or mosaic cell lines.

Absence of ovarian determinant genes, present on both arms of both X chromosomes, results in premature loss of germ cells from the ovaries of patients with Turner's syndrome [5]. Fetuses with Turner's syndrome have as many germ cells at midgestation as do 46,XX fetuses. However, an accelerated loss of germ cells occurs. Many of these individuals lose all of their germ cells before birth. Some lose the remaining germ cells during childhood. Less than 15% of patients with Turner's syndrome lose their germ cells during or after puberty. Of these patients, some will have enough germ cells remaining at puberty to initiate the pubertal process and have regular, cyclic menses during at least a portion of their adolescent or adult years. Less than 5% of patients with Turner's syndrome will ever achieve spontaneous pregnancy before developing ovarian failure [1].

Once the germ cells are depleted from the ovaries, the only remaining tissue present is the connective stroma of the gonads. Having the appearance of "streaks," these residual gonads are called streak gonads. The presence of a Y cell line in a patient with Turner's syndrome brings with it an increased risk of developing gonadoblastomas and malignant germ cell tumors within the streak gonads. Standard dictum suggests surgically removing the streak gonads of these women as soon as a Y chromosome is identified.

Variable stigmata noted in Turner's syndrome patients include cardiovascular anomalies; renal abnormalities, such as horseshoe kidney; high arched palate; low hair line; webbed neck; multiple pigmented nevi; short fourth metacarpals; shield chest; increased carrying angle of the arms; and lymphedema. Virtually all patients are less than 62 inches in height after epiphyseal closure. Several regions of the X chromosome have been implicated for housing height genes. One set of these genes has been identified on distal Xp, the SHOX gene. Absence of the SHOX gene meets the criteria for causing the short stature of Turner's syndrome [6,7]. Autoimmune disorders, such as Hashimoto's thyroiditis, are common, while diabetes is encountered less frequently [8,9].

Cardiac abnormalities include the presence of coarctation of the aorta in up to 30% of patients [1]. A small percentage of patients develop dilatation and potential rupture of the ascending aorta [10]. It is recommended that a cardiac echography be performed every 3 to 5 years. Turner's syndrome patients with primary or premature ovarian failure previously were considered sterile. With the availability of donor oocytes, now it is possible for these women to become pregnant. The question remains, however, whether assisted reproductive technologies should be used to facilitate pregnancy in women predisposed to lethal

cardiac conditions that may be exacerbated during pregnancy. The recent deaths of Turner's syndrome women from aortic dissection and rupture during pregnancies that resulted from donated oocytes demonstrate that this potential cannot be taken lightly [11].

A detailed discussion of Turner's syndrome is presented elsewhere in this issue.

46,XX gonadal dysgenesis

Gonadal dysgenesis in the presence of normal sex chromosomes can be inherited or acquired. Likely the most common cause of primary ovarian failure is autoimmune in nature. Along with primary amenorrhea, these patients are at increased risk for developing other autoimmune abnormalities, such as Hashimoto thyroiditis, hypoparathyroidism, adrenal insufficiency, and pernicious anemia. They should be screened routinely for hypothyroidism and other endocrinopathies as symptoms develop. If a patient is hypothyroid, adrenal insufficiency should be considered before initiating thyroid replacement therapy; otherwise, an adrenal crisis might be precipitated. Recent evidence suggests a diagnosis of adrenal insufficiency is unlikely in the absence of symptoms, such as hyperpigmentation, weakness, lethargy, anorexia, nausea, vomiting, and less frequently, diarrhea and weight loss, which may be impressive. Nearly all patients have hypotension accompanied by orthostasis. Hyperpigmentation, the most consistent feature of primary adrenal insufficiency, is generalized (including mucous membranes), increased specifically in sun-exposed body areas, and accentuated over joints. Given the autoimmune nature of the condition, from 7% to 17% of patients have vitiligo. To ensure a normal adrenal reserve, one must obtain either a random or a stimulated serum cortisol level greater than 17 μg%. Often it is easier to perform an ACTH stimulation test and measure serum cortisol 1 hour after an intravenous bolus of 1 ampule of cortrosyn than to hope for an adequate cortisol level from blood drawn on a random morning. It would not be uncommon for an individual with a normal adrenal reserve to have a random morning cortisol level less than 17 mcg%.

Other acquired causes of 46,XX ovarian failure include radiation, chemotherapy, and environmental causes. Patients previously treated for childhood malignancies, such as Wilms tumor, may develop germ cell depletion as a result of radiation or chemotherapy. Environmental causes, such as childhood viruses, also may cause premature depletion of oocytes. This situation is suspected in identical twin sisters reported to be discordant for ovarian failure [12]. For example, mumps is known to cause orchitis in males, and it is suspected of causing oophoritis and loss of oocytes [9].

Rarely do patients with normal sex chromosomes have a suspected autosomal cause of gonadal dysgenesis and primary amenorrhea [13]. In particular, an autosomal-recessive form of this disorder is apparent in siblings in which nontwin sisters are affected with ovarian failure [1]. Other genetic disorders, such as myotonia dystrophica, ataxia telangectesia, galactosemia, and mucopolysaccharidoses, also have been associated with primary ovarian failure [9].

Recent molecular evidence has identified several X-chromosome loci that seem to be or to influence the ovarian-determinant genes. These loci are POF1 and POF2 [14–16]. In addition, expansion of the triple nucleotide repeat region of the fragile X loci has been identified as a cause of premature oocyte depletion [17].

Pseudo-ovarian failure

Other molecular defects causing an elevation of gonadotropins and hypogonadism in patients with a normal reserve of oocytes have been identified. While such patients are classified as having hypergonadotropic hypogonadism, they do not truly have ovarian failure. FSH receptor gene mutations have been identified in patients previously described as having resistant ovarian syndrome (Savage syndrome) [18–20]. Additionally, patients with 17-hydroxylase gene mutations and luteinizing hormone (LH) receptor gene mutations may present with elevated gonadotropins in the presence of a normal germ cell reserve [21–23]. For patients with these molecular defects, future therapies may be designed to obtain oocytes for pregnancies achieved by way of ART.

46,XY gonadal dysgenesis

Rarely, patients present with 46,XY gonadal dysgenesis (Swyer syndrome). Some of these patients have mutations in the SRY gene that initiate testicular development in utero, suggesting these patients may have mutations in genes expressed upstream or downstream to SRY that affect the process of testicular morphogenesis [24,25]. The facts that virtually all 46,XX true hermaphrodites do not have SRY gene sequences and that individuals with camptomelic dwarfism also have a form of 46,XY sex reversal are evidence that such genes exist in the pathway of testicular morphogenesis [26]. Uncovering the molecular defect responsible for the majority of patients who do not have SRY mutations will provide more details about the critical steps of testicular morphogenesis.

Like other gonadal dysgenesis patients, Swyer syndrome patients develop streak gonads; the testes never form. As a result, they do not produce mullerian-inhibiting substance to ablate the developing mullerian system. They develop a normal vagina, uterus, and fallopian tubes. They do not produce androgens to allow for masculinization of the external genitalia.

For these patients, germ cell loss is complete before birth. At puberty, this lack of germ cells and accompanying steroidogenesis prevents pubertal development; gonadotropin levels are elevated. Patients with Swyer syndrome are often tall because of the height genes present on the Y chromosome. The presence of the Y chromosome places these women at the highest risk of any individuals with gonadal dysgenesis for developing germ cell tumors of the streak gonads. Similar to women with Turner's syndrome who harbor Y-chromosome material, the streak gonads must be removed. Rarely, patients will have germ cell tumors, which secrete significant amounts of sex steroids and confuse the presentation because of associated pubertal development [27].

Hypogonadotropic hypogonadism

Women with primary amenorrhea and hypogonadotropic hypogonadism usually present with delayed puberty as well. In these patients, some process has interrupted GnRH secretion from the hypothalamus or FSH and LH secretion from the pituitary. Such disorders include congenital disorders, constitutional delay, acquired abnormalities, and systemic illnesses.

Congenital abnormalities

The third most common cause of primary amenorrhea (see Table 1) is idiopathic hypogonadotropic hypogonadism (IHH). These patients always have low gonadotropins, previously presumed to be due to lack of stimulation from hypothalamic GnRH. Many respond to exogenous administration of GnRH to initiate puberty and menstruation [28]. While GnRH gene mutations have never been identified in these patients, recent studies demonstrate that some of these patients have mutations in the GnRH receptor gene [29–33]. These patients do not respond to pulsatile GnRH but ovulate after follicular maturation with gonadotropin (FSH and LH) therapy.

A subset of patients with isolated deficiency of GnRH may have Kallmann syndrome. These patients present with hypogonadotropic hypogonadism, hyposmia or anosmia, midline facial defects, and occasionally, renal agenesis. A number of patients have mutations in an X-linked recessive gene (KAL gene), which encodes an adhesion molecule [34]. Due to the lack of this adhesion protein, GnRH-containing neurons do not migrate from the olfactory placcode to the medial basal hypothalamus during fetal development. The ensuing hypogonadotropism is anatomic rather than due to GnRH deficiency. KAL gene mutations have not been identified in females with hypogonadotropic hypogonadism [35]. For men identified with these mutations, unilateral renal agenesis is common.

Other congenital defects associated with primary amenorrhea in girls with hypogonadotropic hypogonadism include DAX1 gene mutations, FSHβ gene mutations, congenital forms of hypopituitarism, and genetic disorders, such as Prader-Willi syndrome and Laurence-Moon-Biedl syndrome [36–38].

Constitutional delay

Individuals with pure constitutional delay of puberty will go through puberty at a time greater than 2.5 standard deviations from the mean. For some, menses will occur within the expected timeframe, while others will meet the definition of primary amenorrhea (see Table 1). Patients with constitutional delay often have a family history of delayed puberty. They are often shorter than their peers, and their bone age lags behind that of their peers. When their bone age reaches 9 to 11 years, they will enter puberty. Most of these patients present between 13 and 16 years of age with some evidence of very early gonadal steroid production. Usually, they have small breast buds (early Tanner stage II development). They have low gonadotropin levels, and if given intravenous GnRH, they will not

demonstrate the prepubertal pattern of gonadotropin release, which is a greater release of FSH compared with LH. Rather, they will demonstrate the presence of a pubertal response (ie, greater release of LH than FSH) [39]. This pubertal response suggests puberty is in its very early stages. An ultrasound study that demonstrates an ovarian multifollicular appearance representative of early puberty is likely as reassuring as the FSH response of a GnRH challenge test for this diagnosis.

Occasionally patients are misdiagnosed with constitutional delay and categorized as "late bloomers," when, in fact, a real disorder may exist. The "quick" presumptive diagnosis of constitutional delay in young female adolescents has been taken from studies of males with delayed puberty in which constitutional delay is reported to exist in 60% of the presenting males. Numerically, constitutional delay is much less frequently diagnosed, ranging from 6% to 30% of young women evaluated [2,40]. Given that puberty is reportedly occurring earlier for American girls, one should be vigilant in making the diagnosis by excluding irreversible reproductive disorders, such as those described above.

Acquired abnormalities

A number of acquired abnormalities may interfere with either the production of GnRH or gonadotropin secretion, producing a hypogonadotropic hypogonadal state. Endocrine disorders, such as hypothyroidism, congenital adrenal hyperplasia, and Cushing's syndrome, which begin before or during early puberty may prevent gonadotropin secretion and may present with primary amenorrhea. Treatment of these disorders usually allows resumption of puberty and menstruation.

The development of pituitary tumors also may interfere with puberty. The craniopharyngioma usually develops between ages 6 and 14 years, causing primary amenorrhea in addition to delayed puberty. It may be an aggressive tumor that causes early destruction of the pituitary and suprasellar regions. Conversely, it also can be an indolent tumor with patients not presenting until their late teens or mid-20s. Usually these tumors are calcified and easily diagnosed radiologically. It was once felt that craniopharyngioma was the most common tumor associated with pubertal menstrual abnormalities. However, it now seems that prolactinoma outnumbers craniopharyngioma as a cause of hypogonadotropic hypogonadism in this age group [1].

Unlike craniopharyngioma, prolactinoma usually does not develop until after puberty is initiated. The increased production of estrogen during early puberty seems to initiate the elevation of prolactin. Estrogen is known to increase messenger RNA for prolactin. For these patients, rather than delay the onset of puberty, prolactinoma usually interrupts a pubertal process that began on time. These patients either present with primary amenorrhea or develop amenorrhea after menstrual function is established. These tumors are extremely slow growing and rarely interfere with other pituitary function. If a dopamine agonist

is given to lower prolactin levels, puberty and menstrual function usually will proceed normally.

Systemic illnesses

Systemic disorders also may interfere with normal gonadotropin secretions. Malabsorptive bowel disease is likely the most common of these systemic disorders [9]. Poorly controlled diabetes and poorly controlled childhood rheumatoid arthritis are other examples of disorders that may interfere with gonadotropin production and delay the onset of puberty and menses.

Adolescence is a common time for the development of eating disorders. Patients with anorexia nervosa rarely present before puberty. They often present with amenorrhea either during puberty or after menstrual function is established. Anorexia nervosa is associated with suppression of GnRH release, which reverts to a prepubertal state. Anorexia nervosa is one of the life-threatening amenorrheic states diagnosed during adolescence. A more detailed description of this disorder is provided elsewhere in this issue.

Eugonadism

A number of young women present with pubertal abnormalities along with evidence of ongoing estrogen production. These patients primarily present with delayed menarche after initiating puberty at the normal time.

Anatomic abnormalities

Congenital absence of the uterus and vagina (CAUV)

The second most common cause of primary amenorrhea in girls is CAUV. During intrauterine development, normally the two mullerian anlagen unite in the midline. This process is associated with canalization of the vaginal plate and the fused uterus [41]. Patients with congenital absence of the uterus and vagina (Mayer-Rokitansky-Kuster-Hauser syndrome) have fusion failure of the mullerian anlagen. As a result, they do not have canalization of the vagina. These patients go through puberty at the normal time, but upon examining those who have initiated sexual activity, a short vaginal pouch or absence of the vagina is found.

The pelvic organs usually consist of small uterine remnants attached to normal fallopian tubes and normal ovaries. The endocrine function of the ovaries is normal. Because they are missing a uterus and vagina, these patients will never have menstrual function; rarely, they may have concealed menstruation within uterine remnants [42]. Nearly 30% of patients have concomitant renal abnormalities, the most common being unilateral renal agenesis. From 12% to 50% of patients have associated skeletal abnormalities, scoliosis being the most common [43].

Because the ovaries in these patients are normal, follicular development and ovulation will occur. In vitro fertilization combined with transfer of embryos to a

surrogate uterus is an option that enables these women to have their own biological children. Initial published data of these children have not yet identified a daughter similarly affected with CAUV [44]. This suggests that CAUV is not transmitted commonly as an autosomal dominant trait.

The genetic etiology of human mullerian anomalies has been studied to varying degrees. Previous studies of CAUV from our laboratory include mutation analyses of candidate genes for these patients. Genes studied include cystic fibrosis transmembrane regulator (CFTR) conductance regulator; WNT7A; anti-Müllerian hormone (AMH); anti-Müllerian hormone receptor (AMHR); HOXA10; HOXA13; galactose-1-phosphate uridyl transferase (GALT); PAX2; and Wilms tumor transcription factor (WT1) [45–53]. To date, none of these studies has revealed a convincing genetic association with CAUV.

Other anatomic abnormalities

Other anatomic abnormalities that may present with primary amenorrhea include imperforate hymen and transverse vaginal septum. These patients may have menstrual cycles, but menses are concealed by their anatomic abnormality. Back up of the menstrual effluvium will occur within the upper vagina (hematocolpos) and the uterus (hematometra). Once these obstructing membranes are excised surgically, normal menstrual function usually follows. While these disorders are usually isolated, rare familial cases have been reported, suggesting a genetic cause [54,55].

Intersex disorders

Androgen insensitivity syndrome (AIS)

Patients with AIS present at puberty with normal onset of breast development, but menses is absent. Instead of a 46,XX karyotype, these patients have 46,XY chromosomes [56]. Instead of having ovaries that produce estrogen, they have testes, which primarily produce testosterone. Because of androgen receptor gene mutations, these patients are unable to respond to the testosterone signal with masculinization of the external genitalia in utero and secondary sexual masculinization at puberty. The androgen receptor gene is X-linked [57]. While most of these abnormalities present in pedigrees with large numbers of affected individuals, these gene mutations can also arise de novo [58].

It was hoped that AIS could be diagnosed by identifying one of a few specific androgen receptor gene mutations. However, most of the mutations identified are unique to the family in which they are found. These mutations are present in all parts of the gene and now explain the differences in results previously published for androgen-binding assays. Mutations in the steroid-binding domain are associated with absent androgen binding. Mutations in the DNA-binding domain are associated with normal binding of androgens to the receptor [59].

At birth, these patients have a normal female phenotype with a small, blind-ending vaginal pouch. At puberty, their increasing levels of androgens are

converted to estrogens with normal female breast development. Patients with complete androgen insensitivity have almost complete absence of pubic hair. Because of the presence of the Y chromosome and its associated height genes, patients with AIS are tall. These patients also have a risk for developing malignancies of their gonads. Because the gonads are testes rather than dysgenetic gonads, the risk of transformation does not increase until after puberty and usually involves the development of seminomas, unlike the germ cell tumors of dysgenetic gonads. Unless these testes are inguinal in location, they are usually left in place until after breast development is complete.

The resistance to androgens in these patients helps us understand the role androgens play in processes such as masculinization. These patients also provide evidence that testosterone likely has an influence on bone formation and reformation. For these patients, conversion of testosterone to estrogen is responsible for the normal timing of epiphyseal closure. However, many of these patients have been reported to be osteopenic, which suggests that testosterone directly influences bone mineral mass. Both testosterone and estrogen receptors have been identified in bone [60,61].

Polycystic ovarian syndrome (PCOS)

While PCOS more commonly causes secondary amenorrhea, it can present with primary amenorrhea. A detailed description of this syndrome is described elsewhere in this issue. The chronic anovulation of PCOS may present initially with primary amenorrhea. As more is learned about insulin resistance in these patients and as better insulin-sensitizing agents become available, it is likely that management will include long-term treatment with insulin-sensitizing agents to decrease adverse health risks (menstrual disturbances, infertility, hirsutism, glucose intolerance, and cardiovascular disease) associated with PCOS.

Summary

Reproductive medicine has changed dramatically since the 1981 publication of the study of patients presenting with pubertal amenorrhea. The breakdown of causes likely remains unchanged, with the four most common causes of primary amenorrhea being ovarian failure (48.5%), congenital absence of the uterus and vagina (16.2%), GnRH deficiency (8.3%), and constitutional delay of puberty (6.0%).

In the study of patients reported by Reindollar, 60% of patients had barriers to reproduction [2]. Since its publication over 15 years ago, developments in assisted reproductive technologies have enabled pregnancy in many of these patients. Women with ovarian failure may gestate pregnancies from donated oocytes. Women with congenital absence of the uterus and vagina may have their fetuses carried in a surrogate uterus.

During this period, the advances of molecular medicine have provided a better understanding of the etiologies of many of these disorders, including Turner's syndrome; 46,XY gonadal dysgenesis; 46,XX gonadal dysgenesis; hypogonadotropic hypogonadism; enzyme-deficient states; gonadotropin resistance; and androgen insensitivity.

Contemporary issues related to these disorders involve information about molecular defects and outcome of pregnancies for patients previously considered sterile. Largely, this information has been extremely helpful and reassuring. However, the reported deaths of patients with Turner's syndrome who become pregnant by donor oocyte should remind us to proceed cautiously as new reproductive avenues are opened for these patients.

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Turner syndrome in adolescence

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Turner syndrome results from the haplo-insufficiency of some or all genes on the X chromosome. This condition may result from the complete absence of one X chromosome or from structural anomalies of one X chromosome. The resulting phenotype is variable and related to the underlying chromosomal pattern. While the classic karyotype related to Turner syndrome is 45,X, the majority of those affected actually have a mosaic chromosomal complement, most often with a second, normal cell line (eg, 45,X/46,XX or 45,X/46,XY) [1]. Some individuals may have more than two different cell lines represented. The actual incidence of chromosomal mosaicism is not known. It is clear, however, that it is more likely to be found if more than one type of tissue is sampled. It also seems that mosaicism is less common in fetuses than in life-born infants, suggesting a survival advantage for affected fetuses with chromosomal mosaicism [2].

The incidence of Turner syndrome among liveborn infants is approximately from 1 in 2000 to 1 in 5000 [3]. In comparison, its incidence in fetal life is roughly 3%. The discrepancy is because an estimated 99% of fetuses affected by Turner syndrome do not survive to term. Turner syndrome is the most common specific chromosomal abnormality found in spontaneously aborted fetuses, occurring in up to 15% of cases [4].

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Turner syndrome is often diagnosed prenatally or in childhood. However, the initial diagnosis may be made at the time of expected puberty or later. All physicians treating adolescent patients need to be able to recognize and accurately diagnose Turner syndrome. For those who follow affected patients, management includes counseling, ongoing screening for associated conditions, and treatment of existing associated conditions.

Definition and diagnosis

Definition

Also known as Ullrich-Turner syndrome, Turner syndrome is defined as a combination of karyotypic findings (the loss of all or part of one sex chromosome) accompanied by characteristic phenotypic features [5].

Diagnosis

A prenatal diagnosis of Turner syndrome has followed a routine screening chorionic villus sampling (CVS) or amniocentesis indicated by advanced maternal age, although the risks of Turner syndrome is not felt to be increased by advanced maternal age. Maternal serum screening is not indicated as a screening tool for Turner syndrome, but it has detected some affected fetuses [6]. In aneuploid pregnancies, the typical finding is increased maternal serum alpha-fetoprotein, human chorionic gonadotropin, estriol, and inhibin A [7]. Occasionally, genetic testing is performed due to a familial history of genetic disorders or due to suspicious ultrasound findings. Typical prenatal ultrasound findings in a fetus with Turner syndrome include cystic hygroma, generalized edema, nonimmune hydrops, increased nuchal translucency, horseshoe kidney, coarctation of the aorta or other left-sided cardiac anomalies, brachycephaly, relatively short limbs, growth retardation, and polyhydramnios or oligohydramnios [3,5,7,8]. All prenatal diagnoses of Turner syndrome should be verified postnatally. Phenotype is not well predicted by genotype, particularly in the case of mosaicism [7].

Diagnostic investigation should include a probe for Y-centromeric material [9]. This may require probing several tissues [7]. Some patients with Y-chromosome material may not show any signs of virilization [9]. The risk for gonadoblastoma or malignant germ cell tumors in the presence of Y-chromosome material may be as high as 30%, although recent reports suggest the incidence is 7% to 10% [10]. If Y-chromosome material is identified, gonadectomy is the standard care [9,11].

Diagnosis of Turner syndrome in infancy, childhood, adolescence, and adulthood is usually suggested by clinical features and confirmed by karyotype analysis.

Clinical aspects

Prenatal

The prenatal clinical features of Turner syndrome are described above. The findings of cystic hygroma and nonimmune hydrops fetalis are characteristic of Turner syndrome and make the diagnosis more likely [5,7].

Infancy

In the newborn and infant, the diagnosis of Turner syndrome should be suspected in the presence of a low posterior hairline, micrognathia, low-set ears, nuchal folds, edema of the hands or feet, or left-sided cardiac anomalies. The karyotype should be assessed if any of these features is present [5].

Childhood

The most common feature of Turner syndrome in childhood is decreased growth velocity. Short stature, less than the tenth percentile for age, is almost universal [3]. Any of the findings in infancy may be seen also in childhood. In addition, many other stigmata of Turner syndrome may be present. Very common are a broad chest with inverted or hypoplastic nipples, a webbed neck, cubitus valgus, knee anomalies, short fourth metacarpals or metatarsals, nail dysplasia, pigmented nevi, abnormal dermatoglyphics, and hearing loss (Table 1) [3]. Many occasional abnormalities are seen also.

Adolescence

The most recognizable signs of Turner syndrome in the adolescent are short stature and pubertal failure. In a multicenter study, the Italian Study Group for Turner Syndrome collected data on 522 patients ages 12 years and older with Turner syndrome [12]. In a normal population, at least 50% of girls show some pubertal development before their 12th birthday [13]. The study showed that 16.1% of girls had complete, spontaneous puberty with menarche. An additional 6.5% had begun spontaneous puberty with breast budding only at the time of inquiry. A further 10.9%, who had begun spontaneous puberty, subsequently experienced arrested development and required estrogen-progestin supplement. In 17.6% of patients, neither spontaneous breast development nor treatment had begun. The largest subgroup (48.6%) had totally induced puberty.

When these patients were analyzed with respect to the influence of karyotype, only 9.2% of patients with a 45,X karyotype experienced complete spontaneous puberty. The highest proportion of patients experiencing complete spontaneous puberty with menarche (40.6%) was in the subgroup of patients with 45,X mosaicism, in which the second cell line had no structural anomalies of the X chromosome.

Table 1
Abnormalities seen in Turner's syndrome

Anomaly	Frequency
Ovarian dysgenesis	>90%
Congenital lymphedema	>80%
Shield chest/hypoplastic nipples	>80%
Anomalous auricles (prominent)	>80%
Facies	
Narrow maxilla (palate)	>80%
Small mandible	>70%
Inner canthal folds	>40%
Neck	
Low posterior hairline/short neck	>80%
Webbed neck	50%
Skeletal	
Elbow anomaly	>70%
Knee anomaly	>60%
Short forth metacarpal/metatarsal	>50%
Bone dysplasia	>50%
Nail abnormality	>70%
Skin	
Pigmented nevi	>50%
Distal palmar axial triradii	>40%
Renal anomaly (eg, horseshoe kidney)	>60%
Cardiac	
Bicuspid aortic valve	30%
Coarctation of aorta	10%
Perceptive hearing impairment	>50%
Hypothyroidism	10%–30%
Ptosis	16%

Modified from XO syndrome (Turner syndrome). In: Jones KL, editor. Smith's recognizable patterns of human malformation. 5th edition. Philadelphia (PA): W.B. Saunders; 1997. p. 81–83 and Jones KL, Health supervision for children with Turner Syndrome. In: Committee on Genetics, editor. American Academy of Pediatrics (RE9543). Pediatrics 1995;96(6):1166–73.

Older studies have suggested a lower incidence of menarche of 5% to 8% [14–16]. However, despite the more recent estimate that 16% of patients with Turner syndrome will experience spontaneous menarche, secondary amenorrhea is common and spontaneous pregnancies are rare, occurring in approximately 2% of women [14,17]. Patients with a single 45,X cell line are less likely to be fertile than those with mosaicism [18]. Of those patients who achieve spontaneous pregnancy, many will abort spontaneously (29%). An estimated 7% will experience a stillbirth, and 34% of live newborns may have malformations, including Down syndrome and Turner syndrome (together seen in 66% of fetuses with malformations) [17]. The seemingly higher incidence of Down syndrome is likely ascertainment bias and unrelated to maternal Turner syndrome. Also seen in increased proportion are spina bifida and congenital heart disease [8].

The adolescent also may experience an increase in the frequency of pigmented nevi, which may not be prominent in childhood. Melanoma is rare, and cosmetic

appearance is the main concern [3]. Treatment may be complicated by the development of keloid scarring, which is common in Turner syndrome. Scoliosis may become evident in the adolescent period, as may insulin resistance and hearing deficits. The adolescent may be at increased risk for inflammatory bowel disease and anorexia nervosa [8].

Adulthood

A previously undiagnosed woman with Turner syndrome may present rarely with premature ovarian failure. Because of the high incidence of hypergonadotropic hypogonadism in Turner syndrome, adult women are prone to develop osteoporosis and cardiovascular disease. They often develop hypertension and type II diabetes mellitus. Thyroid disease, sensorineural hearing loss, and obesity tend to worsen in adulthood [8].

Management

The management of Turner syndrome in adolescence is complex and requires the simultaneous treatment of many different conditions. The adolescent period presents challenges in the management of growth promotion, pubertal development, associated medical conditions, and psychosocial adaptation.

Growth

Short stature affects 95% to 100% of individuals with Turner syndrome [3,5,9]. Up to the age of 3 years, the growth rate is normal, although bone maturation is retarded. Bone age maturation then normalizes until 12 years of age, but growth velocity decreases. Thereafter, both height velocity and bone maturation decrease. In the untreated adult, average height is 140 cm (55 in) ± 13 cm (5 in), approximately 20 cm (8 in) below the mean for the reference population [19,20]. The range around the mean of final height is of similar distribution to that for the normal population. The absence of the SHOX gene on the X chromosome may be responsible for this consistent pattern [20,21]. From the age of 2 years, the child's growth should be followed on the Turner syndrome growth curve (Fig. 1) [3]. If possible, these growth curves should be ethnic-group specific [5]. Children whose growth velocity falls below normal for the Turner growth curve should be referred to a pediatric endocrinologist for investigation of secondary causes of decreased height velocity.

It is now standard treatment in many countries to treat short stature in Turner syndrome with growth hormone [20]. There is considerable evidence supporting the claim that treatment with growth hormone can accelerate growth velocity and increase final adult height [5,20,22,23]. It may even be possible for some patients to achieve a normal adult height [5]. The key elements affecting the success of growth hormone treatment seem to be the age of onset of treatment (inverse relationship), dosage (direct relationship), frequency of administration (direct

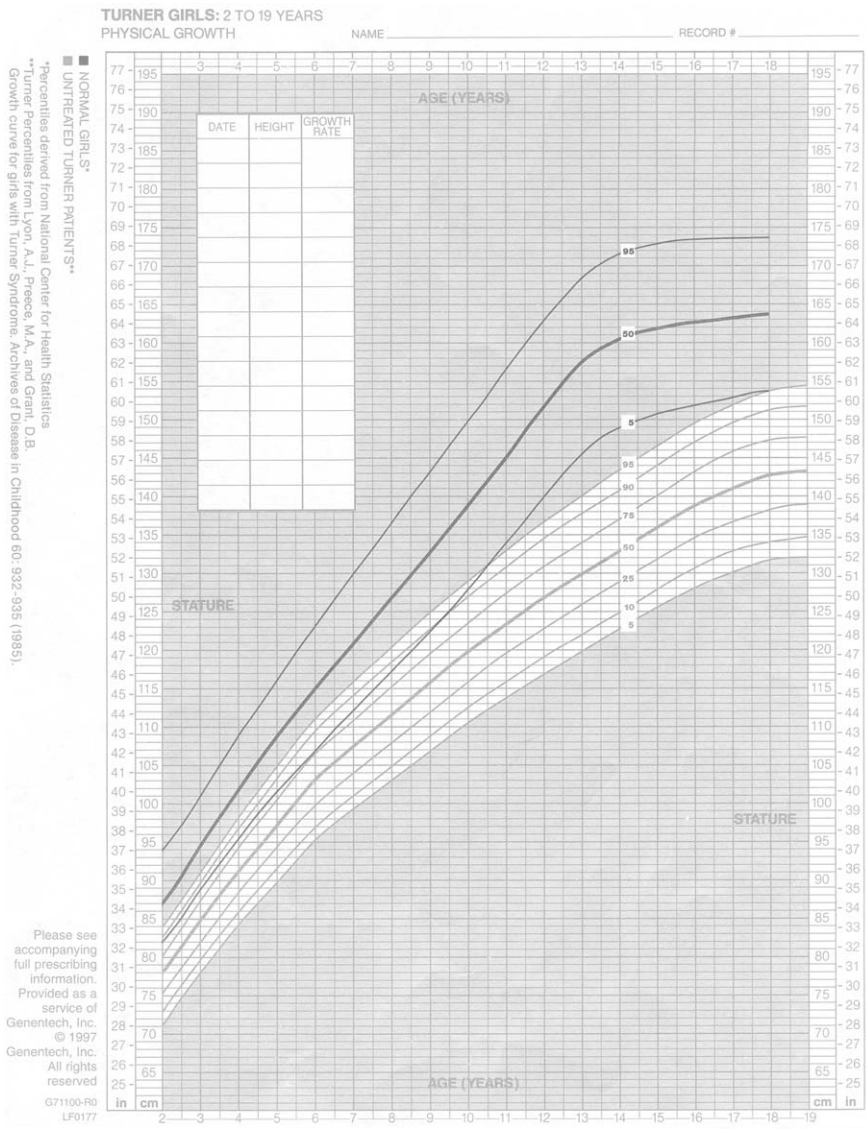

Fig. 1. Turner syndrome growth chart. (Reproduced with permission of Genentech, Inc.)

relationship), concurrent treatment with oxandrolone (direct relationship), patient weight (direct relationship) and distance of height to mean parental height (inverse relationship). In addition, the response to growth hormone in the first year is predictive of response in subsequent years. Karyotype is not predictive of outcome [20].

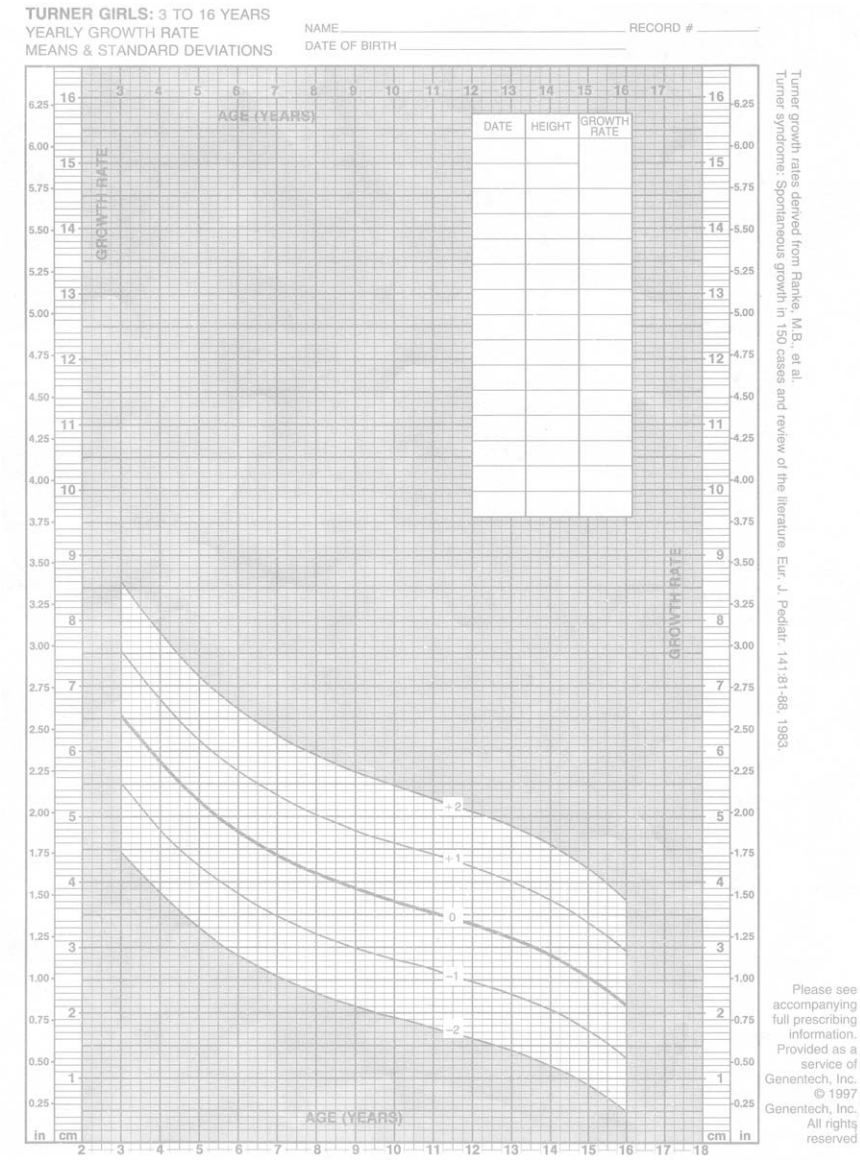

Fig. 1 (*continued*).

The average dosage used to treat Turner syndrome (approximately 0.1 IU/kg/d) is roughly 1.5 times higher than that used to treat patients with growth hormone deficiency [20]. Recently initial dosages of 0.15 IU/kg/d have been recommended for the treatment of Turner syndrome. The dosage should be adapted to patient response [5]. The long-term side effects of growth hormone continue to be

assessed. In 1999, in a randomized-controlled trial, Sas and colleagues treated 68 patients with growth hormone and followed them for 7 years [23]. Eighty-five percent of subjects attained heights within the normal range for the reference population. No adverse events attributable to treatment were reported. Specifically, none of the subjects developed diabetes mellitus, and glycosylated hemoglobin levels remained within the normal range. In a study of 18 patients followed through treatment with growth hormone and oxandrolone, one girl developed overt type II diabetes mellitus more than 4 years following the cessation of treatment. For the other 17 subjects, there was a nonsignificant rise in fasting glucose, a significant rise in the cumulative glucose score (in oral glucose tolerance testing), and a rise in fasting and integrated insulin values. All of these changes were fully reversible upon cessation of treatment [24].

Growth hormone treatment should be administered and followed by a pediatric endocrinologist. Treatment may be instituted as young as 2 years of age and should be started when the patient falls below the fifth percentile of the normal female growth curve for the reference population [5,25]. Early initiation of growth hormone treatment allows maximal duration of treatment prior to the introduction of estrogen replacement [25]. Several studies have shown that estrogen administration diminishes final height attained with growth hormone treatment [25–27]. Estrogen inhibits continued growth because it causes accelerated skeletal maturation and hastens epiphyseal fusion [26]. Treatment for short stature should aim to provide at least 4 years of growth hormone supplementation prior to the initiation of estrogen replacement [28].

Oxandrolone is an anabolic steroid shown to have an additive effect on growth when combined with growth hormone treatment. This androgen is unique in that it is not aromatized into estrogenic metabolites, which would compromise growth. The recommended dosage of oxandrolone is ≤ 0.05 mg/kg/d to avoid androgenic side effects, such as clitoral enlargement and glucose intolerance [5]. It is not recommended for girls under 8 years of age because it may lead to an inappropriate acceleration of skeletal maturation [24]. The addition of oxandrolone may not be indicated; it is best suited to patients in whom growth hormone treatment is not started until 9 years of age or older and in whom bone age is less than 13 years [5,27]. If bone age is 13 years or older, oxandrolone is unlikely to benefit final height [19].

Puberty

Evidence from 45,X abortuses has shown that until at least 14 to 18 weeks' of gestation, the development of the fetal ovary is normal in Turner syndrome. Thereafter, the ovary undergoes accelerated oocyte loss and stromal fibrosis [9]. In normal females, the number of germ cells peak at 20 weeks of gestation at 6 to 7 million oocytes. By birth, an estimated 1 to 2 million germ cells remain. By the onset of puberty, a normal female has approximately 300,000 oocytes, of which 400 to 500 will ovulate [29]. The ongoing process of oocyte depletion progresses over roughly 50 years until the oocyte loses normal function. In Turner

syndrome, this process results in ovarian failure either prenatally or in the first few months to years of life in most patients [9,30]. As a result, Turner syndrome is the most common cause of delayed puberty [15].

Due to abnormal gonadal function, girls with Turner syndrome demonstrate high levels of gonadotropins. While normal girls have slightly elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) for several years after birth, girls with Turner syndrome show a striking exaggeration of this response, especially in the case of FSH [31]. The FSH level begins to decline at approximately 2 years of age, reaching a nadir at near normal levels between the ages of 4 and 10 years. Thereafter, normal girls will have a gradual rise in FSH, whereas girls with Turner syndrome will have a much more marked increase [9].

Although up to 30% of girls with Turner syndrome may experience some signs of pubertal development, most development will be arrested. Estimates of the proportion of girls reaching menarche range from 2% to 16% [5,14,15]. Roughly 2% of women with Turner syndrome will achieve spontaneous pregnancies that are fraught with complications [14,17].

In 1998, Tarani et al reviewed 160 spontaneous pregnancies in 74 patients with Turner syndrome [17]. Of these pregnancies, 29% ended in spontaneous abortions and 7% resulted in stillbirth. No information was available for 6% of pregnancies. Of the 58% resulting in live birth, 34% of infants had malformations. Thirty-four percent of these malformations were multifactorial anomalies. The remaining 66% were Turner syndrome or Down syndrome. The incidence of Turner and Down syndromes at birth, was 15% and 4%, respectively. The incidence in the general population is 0.5% and 0.15%, respectively. Maternal age was not a factor.

The management of puberty in Turner syndrome is related intimately to the management of short stature. A balance must be struck between achieving optimal adult height and inducing puberty at an appropriate age. Some experts suggest delaying estrogen replacement to allow more growth under the influence of growth hormone augmentation [5,26,28]. It is recommended by some that estrogen therapy not be started before 12 years of age or after 15 years of age [5]. The optimal bone age prior to introduction of estrogen is at least 12 years for patients receiving treatment with growth hormone and at least 11 years for others [32].

Before initiating estrogen replacement, the possibility of delayed spontaneous puberty must be excluded. Gonadotropins should be measured, and if normal, the gonads should be assessed with ultrasound [5]. The ovarian volume is higher in patients who will proceed to spontaneous puberty than in those requiring pubertal induction—1.5 cm $\pm$ 0.2 cm^3 and 0.7 cm $\pm$ 0.1 cm^3, respectively [12]. In a small number of patients, the initiation of estrogen therapy may be followed by spontaneous pubertal development. Estrogen replacement must be followed very closely and strictly controlled if a growth spurt, normal or advanced bone age, slight breast development, or measurable serum estradiol levels are seen [32].

When the puberty is induced, it should mimic the progression of natural puberty [5,32]. To allow continued linear growth, initial dosages of estrogen should be very low and increased gradually [5,32,33]. At very low dosages, no obvious signs of puberty may be seen in the first 6 to 12 months [32]. Response to treatment can be

measured by Tanner staging, bone age determination, and uterine growth. To an extent, estrogen dosages can be guided by the patient's response. A reasonable aim is to complete feminization over the course of 2 to 3 years [5].

Several studies have addressed the issue of which formulation of estrogen is most suited to pubertal induction in Turner syndrome. Many years ago, diethylstilbestrol was used and likely resulted in an apparent increase in the incidence of endometrial carcinoma in patients, likely secondary to being used unopposed or sequentially with progestins [9]. Conjugated equine estrogens (CEE), micronized estradiol, and esterfied estrogens [8] are commonly used. Micronized oral estradiol may have an advantage in that, in contrast to CEE, it does not increase hepatic globulins (sex-hormone binding globulin, thyroxine-binding globulin, renin) or blood clotting factors. CEE may lead to a higher incidence of hypertension and thromboembolic disease [32]. In many countries, however, CEE remains the mainstay of treatment. Estradiol may be administered through a patch. Due to the absence of the ''first pass'' through the liver, hepatic effects seem to be less than with an oral preparation, and lower dosages are required for clinical effect [32,34]. Low-dose estrogen formulations may be very difficult to find, although international resources are available [32].

Specific recommendations for estrogen replacement treatment have been suggested by several experts [8,32,33]. Using micronized oral estradiol, treatment may be started at 5 μg/kg/d for 12 months if initial bone age either is 11 to 12 years or is delayed more than 2 years. This dosage is recommended for 6 months if the bone age is greater than 12 years. Following the initial treatment period, the dosage is increased to 10 μg/kg/d for 6 to 12 months. Then the dosage is increased to 15 μg/kg/d for 6 to 12 months, followed by 20 μg/kg/d for 6 to 12 months. Adult replacement levels of 2 mg/d may be started after no more than 12 months at a dosage of 1 mg/d [32]. When CEE is used for pubertal induction, a common starting dosage is 0.3 mg/d for 6 to 12 months, increasing to 0.625 mg/d and gradually to maintenance adult doses of generally 1.25 mg/d [8,33] according to patient response.

To prevent endometrial hyperplasia and carcinoma, cyclic menstruation should be initiated, either through regular estrogen withdrawal bleeding or through progesterone use. When breakthrough bleeding occurs from estrogen treatment, the estrogen dosage may be maintained, but it may be withheld for one week each month to allow withdrawal bleeding. Alternatively, a progestin may be added for 10 to 12 days each month without withholding estrogen. Another approach is to add a progestin between the second and fourth years of estrogen replacement therapy [8,32,33] as opposed to starting it with the onset of breakthrough bleeding.

During treatment, a patient's height, weight, Tanner staging, blood pressure, FSH, and serum estradiol levels should be assessed every 3 to 6 months. Bone age should be measured annually [32]. These parameters will aid in fine-tuning estrogen replacement to mimic natural puberty and maximize growth. Lymphedema, which may be exacerbated by treatment with estrogen or growth hormone, can be monitored [3].

The ideal dosage of estrogen for long-term replacement in adult women with Turner syndrome is not well elucidated. Young women with Turner syndrome do not attain normal peak bone mass, despite receiving estrogen replacement therapy from adolescence [35]. Sufficient dosages are required to prevent the symptoms and sequelae of estrogen deficiency [5]. Increasing dosages often leads to unacceptable side effects, which generally resolve after 1 to 2 months of treatment. Altering the estrogen or progestin formulation may relieve persistent side effects [32].

Associated medical conditions

During adolescence, ongoing surveillance for associated medical conditions is vital. Turner syndrome is associated with a 25% to 50% prevalence of cardiac defects [19]. Among fetuses, the prevalence is closer to 75% [36–39]. The majority of these defects are left-sided anomalies. Bicuspid aortic valve (BAV) is the most common and may be seen in up to 50% of individuals with Turner syndrome [36,37]. Coarctation of the aorta is seen in roughly 30%. Aortic stenosis is seen in 10% of those without BAV, and mitral valve stenosis is seen in less than 3% of patients [36–39]. Less commonly seen anomalies include membranous ventricular septal defect (<5%), atrial septal defect (<5%), partial anomalous pulmonary venous return (5%–10%), and mitral valve prolapse (5%–15%) [36,38,39]. Studies suggest that cardiovascular malformations are more common in individuals with a reported 45,X karyotype and less frequent in those with X-chromosome structural abnormalities [37]. Malformations also seem to be associated with signs of lymphedema, such as webbing of the neck [40].

The most serious consequence related to these cardiovascular anomalies is aortic dissection and rupture [41]. The often fatal complications generally are preceded by aortic dilation involving the root of the ascending aorta [39]. Epigastric or chest pains are typical presenting symptoms that may be misinterpreted as gastrointestinal or pulmonary symptoms. A 4-year-old patient has died from aortic rupture [42]. Most patients with aortic dilatation have risk factors such as BAV, aortic stenosis, aortic regurgitation, hypertension, and obesity. Alarmingly, some patients have no apparent risk factors; thus, all patients need to be monitored regularly for aortic root dilation [39,41].

Patients with a cardiac malformation recognized in childhood require ongoing surveillance by a cardiologist for the development of aortic dilation. When appropriate, they require prophylaxis against spontaneous bacterial endocarditis [39].

If cardiac anomaly has not been detected previously, a cardiology evaluation and echocardiography to screen for aortic dilatation is recommended in adolescence [39]. An MRI also may be useful because it may identify aortic coarctation or dilatation missed by echocardiography [43]. A cardiologist must interpret results in light of a complete physical evaluation. If aortic dilatation is present, follow-up with a cardiologist for repeated imaging should be frequent, perhaps

every 6 to 12 months. If aortic dilatation is absent, a reasonable schedule for repeat echocardiograms is every 3 to 5 years [39].

Tremendous controversy exists over the safety of pregnancy through oocyte donation in Turner syndrome. It is evident that women can achieve pregnancy in this manner, with implantation rates as high as 30% per fresh embryo transferred [44]. However, given the increased cardiac demands of pregnancy, patients with Turner syndrome may have an unacceptably high risk of aortic dissection or rupture and death [45–47]. It appears at least four women died in the third trimester of pregnancy achieved through ovum donation [48–51].

Our 2001 survey of 259 egg donor programs listed in the national Society for Assisted Reproductive Technology (SART) registry uncovered 99 pregnancies from 47% of responding programs [51]. With four reported deaths occurring during this time and likely no more than 200 pregnancies for all programs, an estimated death rate of 2% may be conservative. This alarming finding underscores the need for national guidelines regarding the advisability of pregnancy for Turner syndrome patients. Until guidelines are available, counseling regarding high maternal mortality should begin during adolescent years. Recently discussing the possibility of donor oocyte pregnancies made counseling newly diagnosed adolescents easier, especially when broaching the subject of infertility/sterility. Given the gathering body of evidence about the high maternal mortality rate, it would be better to address the potential dangers of pregnancy from the very first discussions. While identified risk factors for dilation, dissection, and rupture of the ascending aorta should serve as very strong relative contraindications for subsequent pregnancy, the absence of these identifiable risks does not clear the way for a risk-free pregnancy.

Perhaps 30% to 60% of individuals with Turner syndrome have congenital renal malformations. The most common of these are horseshoe kidney and double collecting systems [5,19]. For the most part, renal malformations do not affect renal function [5]. There are reports, however, of patients who develop hypertension, infection, and hydronephrosis [5,9,52]. In addition, case reports describe moderate to severe renal impairment with membranoproliferative glomerulonephritis [53] and focal segmental glomerulosclerosis [54,55]. If ultrasound examination reveals a renal malformation, appropriate treatment should be instituted, and regular ultrasound evaluation and urine cultures should be performed every 3 to 5 years [5].

Turner syndrome carries a significant increase in the incidence of Hashimoto's thyroiditis [3,33]. Individuals with structural defects of the X chromosome may be particularly susceptible to autoimmune diseases, including Hashimoto's thyroiditis, Grave's disease, inflammatory bowel disease, myasthenia gravis, IgA deficiency, and membranoproliferative glomerulonephritis [52,53,55,56]. The overall incidence of hypothyroidism is estimated from 10% to 30%, but it may be as high as 50% in adulthood [8]. Clinical effects of hypothyroidism are often lacking, requiring diligence in screening for a diagnosis. It is recommended that thyroid-stimulating hormone, and possibly free thyroxine and antithyroid antibodies, be assessed every 1 to 2 years [3,5,8]. There is no apparent increase in

the incidence of hypothyroidism before 10 years of age [57]. Prompt treatment of hypothyroidism may deter the development of obesity and hypercholesterolemia [52].

Osteopenia and osteoporosis are common in Turner syndrome [52]. Gravholt et al estimate a relative risk of 10 for osteoporosis in Turner syndrome [58]. Furthermore, the attainment of peak bone mass in young women with Turner syndrome is inhibited, despite treatment with growth hormone and estrogen replacement in adolescence [33,35,52]. Bone mineralization is better in individuals treated with growth hormone and estrogen replacement, but it is suboptimal nevertheless [52]. Osteopenia is not recognized consistently in adolescents with Turner syndrome, but it becomes evident in adulthood [33]. Estrogen replacement does improve bone mineral density and should be used in combination with exercise and adequate calcium and vitamin D intake [33,52].

Approximately 10% of adolescents will develop scoliosis, which must be monitored carefully because it may reduce height [5,8]. Ongoing orthopedic evaluation is important also to evaluate elbow, knee, and hip abnormalities that may cause pain. Turner syndrome increases the risk of congenital hip dislocation, which may predispose the individual to degenerative arthritis of the hip [5,8].

Inflammatory bowel disease (IBD) is increased in prevalence in Turner syndrome and may be as high as 1.5% [19,56,59]. Both ulcerative colitis and Crohn's disease tend to be severe in these patients, who often require early surgery [5]. Gravholt et al showed a trend toward an increased risk of inflammatory bowel disease with a relative risk of 2.25 [57]. IBD should be ruled out in patients presenting with gastrointestinal symptoms, especially unexplained diarrhea and bleeding [52]. The increased risk of ulcerative colitis seems to translate into an increased risk of cancer of the colon and rectum, although the increased risk of cancer of the colon persists in the absence of inflammatory bowel disease [52,57].

Other types of cancer do not seem to be increased in Turner syndrome, with the exception of malignant germ cell tumors (usually dysgerminoma) in Turner patients with Y-chromosome fragments. Y-chromosome material may be seen in up to 6% of Turner patients [9,51]. These tumors may be unilateral or bilateral. Usually they do not metastasize even though they may spread locally [9]. These tumors are occasionally identified in childhood, and the risk increases with age from an estimated 2% at age 10 years to 27.5% at age 30 years [60,61]. Early gonadectomy is recommended to prevent germ cell tumors [9,51].

Gravholt et al also found an increased incidence of hepatic cirrhosis in Turner syndrome with a relative risk of 5.7. The cases were not related to alcohol abuse or hepatitis [58]. It has been shown that many individuals with Turner syndrome have elevated liver enzymes, but the relationship of these elevated enzymes to liver disease has not been established. Estrogen treatment improves the liver enzyme profile [5].

Glucose intolerance is more common in Turner syndrome than in the general population. However, overt diabetes is rare in childhood. Treatment with oxandrolone to promote growth may result in worsened glucose tolerance during the

course of treatment [5,8]. Controversy exists whether women with Turner syndrome are at increased risk for developing overt diabetes [7,8,57]. Gravholt et al found a 4.4-fold increase in the risk of type 2 diabetes and, unexpectedly, an increased prevalence of type 1 diabetes in Turner syndrome patients. This study also suggests an increase in the prevalence of "syndrome X," characterized by type 2 diabetes, hypertension, dyslipidemia, and obesity [7,58]. Some experts suggest the increased incidence of type 2 diabetes is not related directly to Turner syndrome but is due to obesity, which is common in Turner syndrome [8].

Girls and women with Turner syndrome are prone to hearing loss, which may be conductive or sensorineural [3]. Individuals with Turner syndrome are prone to developing otitis media, likely due to the congenital high-arched palate and distortion of the Eustachian tube. Infections are particularly common between the ages of 1 and 6 years and should be treated aggressively because repeated infections may lead to conductive hearing loss [5,8]. The observed sensorineural hearing loss is characterized as a sensorineural dip at a frequency of 1 to 2 kHz and high-frequency loss assumed to be related to an abnormality of the outer hair cells of the lower middle coil of the cochlea [5,7]. Hearing loss is more frequent in individuals with a 45,X or 45,X/46,X,i(Xq) karyotype. It can occur as early as 6 years of age, and it deteriorates with age [5,7]. At any age, the hearing threshold is higher in Turner syndrome [7]. Audiologic evaluation should be routine in the care of girls and women with Turner syndrome [51].

Psychosocial aspects

Certain personality traits have been reported as common in Turner syndrome. These traits include high stress tolerance, limited emotional arousal, high degree of dependence, unassertiveness, and overcompliance [5,7]. However, recent evidence suggests that these features are common in many women with short stature and delayed sexual development who do not have Turner syndrome [5]. Girls with Turner syndrome clearly identify with female gender. The initiation of sexual activity, however, tends to be delayed and infrequent [5,62]. Adequate and timely estrogen replacement seems to be important for self-confidence and may be important for developing appropriate social relations [7]. Patients treated appropriately have higher professional status [63]. One study of 69 Danish women with Turner syndrome demonstrated that their level of education and occupational distribution was similar to that of their unaffected sisters. However, the unemployment rate of Turner syndrome women was higher [64].

Except in the case of individuals with a small ring X chromosome, there is no increase in the prevalence of mental retardation [5,65]. There is evidence showing that certain impairments do affect some individuals with Turner syndrome. Specifically, difficulties have been reported in spatial organization, mathematics, and psychomotor performance for some, but not all, patients with Turner syndrome [5,7]. Some of these deficits may be improved with estrogen therapy [66]. Other suggested abnormalities include hyperactivity, depression, and

anorexia nervosa, along with delayed emotional maturity, poor relations with peers, timidity, and negative body image (Table 1) [7,67,68].

Summary

The management of a patient with Turner syndrome is complex and multifaceted. It is best accomplished by an interdisciplinary approach. Initial diagnosis is generally prenatal or suggested by physical characteristics. Diagnosis should include karyotype analysis and potentially a probe for Y-chromosome centromeric material to assess the risk for the development of germ cell tumors. At the time of initial diagnosis, the patient should be thoroughly investigated for associated medical conditions. Ongoing surveillance for the development of complications is of paramount importance. The interdisciplinary team should include an endocrinologist; cardiologist; nephrologist; reproductive endocrinologist; audiological physician; ear, nose and throat surgeon; plastic surgeon; dentist; and psychologist [5]. It is important to provide to girls and women with Turner syndrome, and their families, comprehensive information about the syndrome and to advise them about the availability of Turner syndrome societies that can provide information and support.

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Abnormal uterine bleeding in adolescents

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Abnormal uterine bleeding is a clinical problem that is encountered frequently during the adolescent years. In the first 5 years after menarche, anovulation that arises from a lack of maturity of the hypothalamic–pituitary–ovarian-axis is the most common cause of such bleeding [1,2]. Other pathologic conditions, such as reproductive tract anomalies, trauma, infections, systemic illnesses, complications of pregnancy, and disorders of coagulation may closely resemble anovulatory bleeding and thus it remains a diagnosis of exclusion. Knowledge of the menstrual cycle, as well as the expected physiologic events that are associated with the perimenarchal period, is essential to develop careful diagnostic protocols and adolescent-specific treatment regimens.

The menstrual cycle

The menstrual cycle represents a complex interrelationship of hormones and physiologic events in the brain, the ovary, and the uterus that prepares the body for the possibility of conception. An understanding of these relationships is essential for any discourse on its irregularities.

The average menstrual cycle lasts 28 days. During this time, key changes occur in the ovary and uterus that will facilitate either implantation of a fertilized ovum or sloughing of the endometrium. These events represent the effects of critical hormones that are secreted by the hypothalamus, the pituitary, and the ovary. This is known as the hypothalamic–pituitary–ovarian-axis (HPO). The menstrual cycle can be separated into two distinct phases, the follicular phase and the luteal phase. The follicular phase begins with sloughing of the endometrium on the first day of the menstrual cycle, and culminates with ovulation. The luteal phase begins with ovulation and culminates with either menstruation or conception.

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The follicular phase lasts approximately 14 days and is marked by the development of ovarian follicles and the initiation of endometrial growth. Estrogen is the predominant hormone of the follicular phase; however, its production is dependent on several other hormones including GnRH, FSH, LH, and inhibin. Gonadotropin-releasing hormone is secreted in a pulsatile fashion from the arcuate nuclei in the hypothalamus. The hypothalamus functions as a pulse generator and GnRH as the regulating hormone that ultimately governs the cyclicity of the menstrual cycle. Ovarian function is dependent on this pulsatile secretion pattern. Interruption of the GnRH pulse generator can lead to disturbances in the menstrual cycle [3]. GnRH travels through the hypothalamic portal plexus to the anterior pituitary where it stimulates the production of the pituitary gonadotropins, follicle-stimulating hormone, and luteinizing hormone. The rate at which FSH and LH are secreted by the anterior pituitary is dependent on the production of the ovarian steroid hormones, estrogen and progesterone, as well as GnRH secretion.

The ovarian follicles are in a constant state of growth and degeneration. FSH and LH are at their lowest levels late in the menstrual cycle; however, approximately 2 days before menstruation the level of FSH begins to rise. Only those follicle that have reached an appropriate stage in development at the time of increasing FSH levels will progress on to further differentiation instead of atresia. Typically, 3 to 11 follicles will be at an appropriate stage of development in any given cycle. FSH, a glycoprotein, acts primarily on the granulosa cells of these follicles to stimulate their continued growth and to increase the number of LH receptors. LH, which is also a glycoprotein, acts primarily on the theca cells of the developing follicles and stimulates androgen synthesis. FSH facilitates the conversion of androgen to estrogen by stimulating aromatase activity within the follicle. As estrogen levels within the follicles increase, the number of FSH receptors on the granulosa cells also increases and the follicles undergo an accelerated growth. Ultimately, the follicle that secretes the highest level of estrogen and exhibits the greatest sensitivity to FSH will become the dominant follicle [4]. The estrogen that is produced by the dominant follicle then functions to decrease the secretion of FSH by the pituitary in a negative feedback loop. Estrogen also stimulates the increased secretion of LH by way of positive feedback. Other hormones that are produced locally by the follicle, including inhibin A and B, also feedback on the pituitary to decrease the production of TSH, whereas activins increase the sensitivity of the follicles to FSH [5]. These actions further insure the continued growth of the dominant follicle at the expense of the other developing follicles. Estradiol levels continue to increase until approximately day 13 or 14 of the cycle; at this time they reach a critical threshold that leads to a marked surge in LH production and ovulation.

The ovulatory portion of the cycle typically lasts 24 to 48 hours and signals the beginning of the luteal phase of the menstrual cycle. The midcycle LH surge triggers ovulation and the expulsion of the oocyte from the dominant follicle. In addition, the LH surge stimulates the oocyte to resume meiosis. In the 24 hours before ovulation, the production of progesterone increases gradually. After

ovulation has occurred, the follicle, in response to the LH surge, transforms into the corpus luteum and predominantly produces progesterone.

The first 3 days of the luteal phase are characterized by increasing levels of progesterone. Eventually, levels reach a steady state that will last for the next 11 days. The elevated level of progesterone that is seen in the luteal phase decreases the production of FSH and LH in the pituitary by negative feedback. In addition, progesterone decreases the pulsatility of GnRH secretion which further decreases the secretion of FSH and LH [6]. In the absence of pregnancy, the corpus luteum will reach the end of its natural lifespan by the fourteenth day of the luteal phase. As the corpus luteum involutes there is a marked decrease in the production of progesterone which leads to the onset of menses. As the progesterone level falls, the inhibition of FSH and LH secretion is removed, the pulsatility of GnRH secretion is renewed, and the cycle begins anew.

The steroid hormones, estrogen and progesterone, have specific effects on the growth and maturation of the endometrium. The endometrium is actively sloughing at the beginning of the follicular phase. Normal menses will last approximately 4 days. As estrogen levels increase in the early follicular phase there is a stabilization of the vasculature and proliferation of the endometrial glands, stroma, and spiral arterioles. Estrogen binds to receptors in the endometrium where it stimulates specific growth factors. After ovulation, and in response to progesterone, there is a rapid change from the proliferative to the secretory state as the endometrium is prepared for implantation. The endometrial glands become increasingly tortuous and produce glycogen-rich secretions. The endometrial stroma becomes decidualized and increasingly edematous with an increased vascularity. Once progesterone support is removed, the endometrium degenerates rapidly; approximately 50% of its mass is passed in the first 24 hours. Vasoconstriction and an improving hormonal milieu ultimately lead to cessation of the menses as the next cycle begins again [7]. In a menstraul cycle in which there has been adequate preparation by the HPO axis, the events should occur in an orderly and sequential pattern. The normal interactions of hormones and histology throughout the menstrual cycle should ultimately lead to an endometrium that is well-prepared for pregnancy or the orderly sloughing of the menses.

Adolescent menstruation

Although the onset of menstrual bleeding is recognized as a pubertal milestone, the hypothalamic–pituitary–ovarian-axis continues to mature after menarche through the first 5 years of the menstrual cycle. Near the time of menarche, the positive feedback influence of estradiol is absent and thus ovulation does not occur [8]. Lemarchand-Beraud et al [9] investigated 90 healthy girls over the first 5 years after menarche [9]. They found that estrogen, progesterone, LH, and FSH values were all below normal adult levels in year one. In year two, estradiol levels increased to normal adult values. By year five, FSH and LH levels had gradually increased to near normal adult values, but serum

progesterone levels indicated that there were still a low percentage of ovulatory cycles (0%–63%). The timing of menstrual cycles is often irregular initially, but become more predictable over time [10]. Menstrual cycles may range from 21 to 45 days in the first 3 years after menarche, although with time a shortening and cyclity of the menstrual cycle is expected [11]. As gynecologic age (ie, the age after menarche) increases, ovulation patterns become more established. McDonough and Gant [12] found that 55% to 82% of the cycles were anovulatory in the first 2 years; by the fourth and fifth years only 20% of cycles were anovulatory. Anovulatory bleeding was the cause in 50% to 74% of patients who were admitted for inpatient stay because of severe bleeding [1,2].

In addition to pure anovulatory cycles, adolescents may experience dysfunctional ovulation with a prolongation of the follicular phase that results in increased cycle length [13]. The aberrancy or absence of ovulation results in an estrogenic endometrium without progesterone influence. The effect of estrogen stimulation, in the absence of progesterone, results in increased fragility of blood vessels within the endometrium and overgrowth of glandular elements with inadequate stoma support. Clinically, the endometrium is at risk to shed irregularly and unpredictably. This may lead to erratic bleeding or heavy, prolonged menstruation.

Differential diagnosis

In adolescents, as with any woman of reproductive age, the possibility of a complication of pregnancy must be initially excluded as a cause of abnormal uterine bleeding. Although the adolescent birth rate is declining in this country, more than 900,000 American teens become pregnant each year; the majority of these pregnancies is unplanned [14]. Teens may be reluctant to admit to the possibility of pregnancy, even with private questioning, so a high degree of suspicion is indicated among all young women who present with troublesome menstrual bleeding.

The character, frequency, and associated presenting symptoms can often suggest the diagnosis (Box 1). Heavy, prolonged, recurrent menstrual periods are not normal adolescent patterns of bleeding and may represent an underlying coagulation defect. In their series, Claessens and Cowell [1] found that 19% of patients who required hospitalization for acute hemorrhage had an underlying coagulation disorder. When the young women had severe anemia associated with menometrorrhagia, the number with an underlying coagulation disorder increased to 28%. Immune thrombocytopenic purpura and von Willebrand's disease were the most common findings.

vonWillebrand's (vWD) disease is an autosomally inherited bleeding disorder that is related either to the qualitative or quantitative production defect of vonWillebrand's factor [15]. Type 1 vWD accounts for 70% of all cases with a 1% to 3% prevalence in the general population [16]. It is generally mild and is diagnosed by a combination of clinical and laboratory findings. In a screening study of women with a history of menorrhagia and a normal examination, 17%

Box 1. Differential diagnosis of abnormal uterine bleeding in adolescents

- Pregnancy related
  - Ectopic pregnancy
  - Threatened abortion
- Disorders of coagulation
  - von Willebrand's disease
  - Factor XI deficiency
  - Glassmans
  - Thrombocytopenia
  - Leukemia (fibrinogen deficiency)
- Endocrinopathies
  - Androgen disorders
    - Polycystic ovarian syndrome
    - Congenital adrenal hyperplasia
    - Androgen-secreting tumors
  - Hyperthyroidism
- Infections
- Trauma
- Systemic disease
  - Renal disease
  - Diabetes
- Disorders of the reproductive tract
  - Leiomyoma
  - Endometriosis
  - Congenital anomalies
  - Cervical polyps

had an inherited bleeding disorder; vonWillebrand's disease and Factor XI disease were most prevalent [17]. This may be especially significant for individuals with a history of menorrhagia that coincided with menarche. Claussens and Cowell [1] found that when severe menorrhagia was associated with the initial menses, 45% of patients had an underlying coagulation disorder. Similarly, in women with complaints of menorrhagia, the onset at menarche was noted in 65% of adult women with bleeding disorders compared with only 8.9% of adult women in whom no bleeding disorder was found [17].

Heavy menstrual bleeding may also be the presenting symptom for acquired disorders of platelet dysfunction including immune thrombocytoplastic purpura, aplastic anemia and leukemia. Bevan et al [18] found a 13% incidence of thrombocytopenia among all girls who presented to a children's hospital for evaluation of menorrhagia.

Anovulatory bleeding is common, but with other manifestations it may signal an underlying endocrine or systemic disease. The presence of severe acne, facial

and other male pattern hair growth, and central obesity may suggest polycystic ovarian syndrome, especially when the symptoms coincided closely with menarche [19]. Prompt recognition and treatment may be important to decrease the risk of complications of hirsutism, cardiovascular disease, and diabetes in later life. Signs of severe hyperandrogenism may be associated with congenital adrenal hyperplasia or other disorders of the adrenal gland. Hypothyroidism may cause menorrhagia and have associated thermoregulatory or metabolic symptoms, whereas hyperthyroidism is usually associated with amenorrhea.

Chronic diseases, such as renal or liver disease, may be associated with menstrual bleeding, especially if end-stage. Fibrinogen and erythropoetin levels may be decreased which leads to long and erratic menses. Patients with chronic diseases may suffer from anovulation and resultant estrogen withdrawal bleeding

Infections may result in erratic or heavy chronic bleeding, particularly when bleeding is associated with significant pelvic pain or tenderness. Sexually transmitted diseases may result in cervicitis and inflammation or endometritis that causes the endometrium to be fragile and shed irregularly. In the United States, young women 15 to 19 years of age have the highest reported rate for chlamydia and gonorrhea [20]. Compared with adults, adolescents are more likely to contract a sexually transmitted disease, to become reinfected, to engage in high-risk sexual behavior, and to have partners who are likely to also have a sexually transmitted disease [21]. In college-aged women who use oral contraceptives, chlamydial infections were significantly more prevalent among those who experienced breakthrough bleeding than among women without breakthrough bleeding [22]. It is important to maintain a high index of suspicion of sexually transmitted diseases among adolescents who complain of problematic vaginal bleeding.

Pain that is associated with bleeding may be a signal for other gynecological diseases. Endometriosis is often considered to be a disease of women in their midreproductive years, but in many cases it may have an earlier presentation. In one series, endometriosis was found in 69% of adolescents who presented with pelvic pain and in 9.4% of those who presented with vaginal bleeding [23]. Leiomyomas, although less common than in adults, may also occur in adolescents and can be associated with disruption of the normal endometrial development [24]. Adolescents occasionally develop other benign polyps and tumors of the cervix and endometrium that can be associated with irregular bleeding; malignant disease is a rare consideration in adolescence.

When pain and intermenstrual bleeding is recurrent, the possibility of a partially obstructive congenital uterine anomaly, such as a transverse septum or uterine horn, must be investigated. These young women most often have regular menses but complain of cyclic pain that is associated with intermenstrual spotting. Because the patient is menstruating, the diagnosis may not be made for several cycles. Ultrasonography and MRI are highly accurate at detailing normal uterine anatomy and are useful in excluding congenital anomalies.

In the presence of severe bleeding, trauma and genital injury must be excluded. Rape, sexual abuse, and consensual sexual experiences can result in

intended or unintended injuries to the genital tract. Young women may also cause injury to themselves with attempts to use tampons or retaining tampons or other foreign objects within the vagina. Most often these injuries are accompanied by discomfort and a foul odor.

Clinical evaluation

Many adolescents are anxious about the gynecological evaluation for abnormal bleeding and may approach their visit with a great deal of apprehension. It is important to realize the complete evaluation of adolescents takes patience and an orientation toward their special needs and concerns. It is helpful to establish a relaxed atmosphere that is respectful of their privacy and emerging autonomy. Boundaries of confidentiality should be discussed at the onset of the visit and the adolescent and her parents should have an opportunity to be interviewed alone as well as together [25].

A complete medical history often provides clues about the cause of bleeding. It is important to discuss overall general health and other health problems. All surgeries should be reviewed, especially the details of surgeries such as dental procedures or minor injuries that may have been associated with complications. Growth patterns and pubertal milestones including breast and pubic hair development, growth spurts, and menarche should be recorded.

A detailed month-by-month account of menstrual periods including duration, quantity, and quality of flow, associated pre- and menstrual symptoms of vaginal secretions, pelvic pain, cramping, mood changes, and other cyclic, physical changes should not be overlooked. Many adolescents are concrete thinkers and the concept of ''monthly'' flow can only be normal if it is confined to one episode per calendar month. The use of a graphic, such as a menstrual diary, is very helpful. Many adolescents do keep track of their menstrual periods in this fashion and it should be solicited if available. Quantity of flow is often difficult for the adolescent to reliably communicate. Among adult women there is no correlation between pad use and actual menstrual loss [26]. Instead of pad counts, it is often more helpful to focus on details such as number of overflow pads during class time or at night, number of hours each pad is worn, type of pad. The need to wear multiple pads or to refrain from activities for fear of overflow is an indicator of heavy flow.

A sexual history is an essential part of the questioning in all adolescents. It is important that these questions are asked in a nonthreatening way and in an environment in which the teen will feel comfortable giving a candid response. Even if the teen is not sexually active, it gives the opportunity to discuss sexuality issues and other issues of interest to teens. It is often helpful to begin by explaining the high prevalence of sexually transmitted diseases and pregnancy and their relationship to abnormal bleeding. This can often open the dialogue to the importance for looking for these infections for at-risk teens.

The review of systems should include questions about bleeding, especially from the gums, and general metabolic parameters, such as change in exercise

endurance, heat and cold tolerance, and overall sleep patterns. A body weight history should be taken and any rapid changes in body weight should be noted.

The family history should include information about any family members that may have known bleeding disorders, hemorrhage, or other surgical or obstetric bleeding complications. It is often helpful to ask if any female relatives had problem menstrual periods that required intervention and to establish a pedigree of several relatives.

A careful physical examination is essential in the adolescent with problematic bleeding. Vital signs should always be obtained. In the presence of severe bleeding, tachycardia, especially in association with pale sclera, pallor, or postural dizziness may establish the need for emergent resuscitative care. A height and weight and calculation of body mass index should be obtained as a part of the vital signs.

The examination of the major body systems, especially the skin and neurologic system can provide clues of endocrinologic and systemic diseases. Petechial hemorrhage or ecchymosis should be searched for if a bleeding disorder is suspected. Tanner staging of the breast and pubic hair should always be assessed as it serves as a hormonal marker for the presence of estrogen and androgen hormonal influence at some point in development. The presence of excessive androgen stimulation, such as severe acne, terminal hair growth on the lower jaw, chin, or lip, hair in the midline chest or back, or in a male pattern on the lower abdomen should be noted.

The inspection of the genitalia and introital opening is an essential part of the examination to identify trauma, genital tumors, or anomalies. Further examination must be tailored to the age and clinical situation of the adolescent. Because of the anxiety many adolescents and their parents feel about genital and pelvic examination, adequate time for explanation and patience and gentleness during the examination is essential. In a young patient who has not initiated sexual intercourse, a speculum examination may not be necessary in the absence of heavy acute bleeding, pain, or associated gynecological symptoms. If sexual activity is suspected, cultures for sexually transmitted diseases are indicated. If a speculum examination is appropriate to the differential diagnosis in her clinical situation, a young adolescent can be adequately examined using a narrow, straight blade speculum (Fig. 1). These speculums are 5/8 inch wide, but have the advantage of a 4-inch length that will allow visualization of the cervix. A single digit or a recto-abdominal examination can be gently performed if necessary on most adolescents to assess the pelvic contents for masses or alteration in pelvic anatomy.

A pregnancy test should be the initial laboratory test before beginning any assessment (Box 2). A complete blood count with a differential and a platelet count is essential in the evaluation of the adolescent with abnormal bleeding. Additional testing should be based on history and physical findings that indicate the possibility of other diseases and should be drawn before instituting any hormonal or blood component therapy. If the bleeding is excessive, the patient is anemic, or the symptoms have occurred since menarche, further evaluation for a

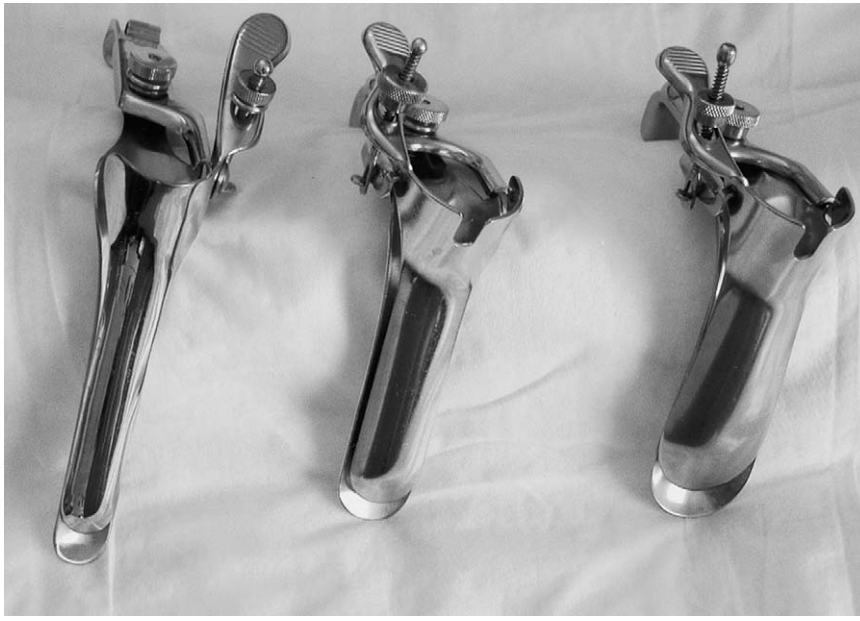

Fig. 1. Huffman speculum (far left) compared with Pederson and Graves speculums.

Box 2. Laboratory assessment of severe bleeding

Initial evaluation

Complete blood count and differential
Platelet count
Fibrinogen
Prothrombin time
Partial thomboplastin time
Bleeding time

If bleeding is severe or prolonged or associated with menarche or if the initial screen in abnormal

von Willebrand's factor antigen
Factor VIII activity
Factor XI antigen
Ristocetin C co-factor
Platelet aggregation studies

bleeding disorder should be performed. Bleeding studies, including prothrombin time, partial thromboplastin time, and bleeding time, should be ordered. If any of these baseline tests are abnormal or if there is a strong clinical suspicion of a bleeding disorder, then further laboratory analysis should be undertaken. Factor VIII antigen activity, ristocetin co-factor, platelet aggregation, Factor XI, and vonWillebrand's Ag assays should be drawn. Consultation with a hematologist may be helpful to further evaluate for bleeding disorders, as the assays may need to be repeated on multiple occasions to arrive at the diagnosis.

In the presence of signs or symptoms of systemic or metabolic disease, testing for thyroid, adrenal, or other systemic disease may be indicated. If the adolescent has associated hyperandrogenism, serum testosterone, dehydroandrosteindione sulfate, and 17-hydroxyprogesterone levels may be obtained to evaluate the source of the androgen. Fasting insulin and glucose level and gonadotropin levels may be indicated to evaluate the disease and help to tailor therapy (see elsewhere in this issue).

Ancillary procedures, such as transabdominal ultrasound, occasionally provide additional information if the examination is incomplete or the bleeding is atypical. In the presence of prolonged bleeding, severe hyperandrogenism, or obesity endometrial sampling may be indicated. Endometrial atypia, and even carcinoma, although rare, have been described in the adolescent population [27]. If a uterine anomaly is suspected, transperineal ultrasound or magnetic nuclear imaging may be helpful in defining the abnormal anatomy.

Treatment

Treatment goals for adolescents with abnormal bleeding are to identify the source of the bleeding and direct therapy towards the cause, to stop abnormal bleeding, and to help the adolescent have more predictable, manageable menstrual cycles. Immediate treatment strategies can be categorized based on the severity of bleeding (Box 3). If the adolescent is bleeding profusely, is hypovolemic, or has a hemoglobin less than 9gm/dl hospitalization and immediate resuscitation with volume expansion and possible blood products is indicated. As discussed earlier, it is essential to obtain blood samples to evaluate for underlying disease before instituting therapy.

Hormonal therapy remains the most effective therapy in adolescents; more than 93% respond medically to treatment [1]. Intravenous administration of conjugated equine estrogens (Premarin) (25 mg every 4 hours) is highly effective in controlling uterine bleeding. In one clinical trial, two injections of intravenous Premarin stopped severe uterine bleeding in 72% of subjects compared with 38% of patients who were given placebo [28]. The immediate action seems to be small vessel hemostasis through direct effect on clotting, including increasing production of fibrinogen, Factor V and IX activity, and platelet aggregation [28]. Long-term use of Premarin allows proliferation of denuded areas of endometrium. Intravenous therapy is associated with nausea and vomiting in some individuals

Box 3. Management of abnormal uterine bleeding in adolescents

Severe bleeding (prolonged, heavy bleeding with anemia, hemoglobin < 9 gm/dl, hypovolemia)

- Resuscitation with intravenous fluids, blood products as necessary
- Evaluation for underlying disease, especially coagulation defect
- Immediate treatment with intravenous equine estrogens
- Consideration of long-term, oral, hormonal support

Moderate bleeding (menses prolonged, heavy or interfering with daily activities, menses interval marked shortened or mild anemia present)

- Oral equine estrogen or combination oral contraceptives in accelerated dosing
- Cyclic progesterone or combination oral contraceptives for 3 to 6 months after bleeding is controlled

Mild bleeding (menses mildly prolonged or irregular, no evidence of anemia)

- Reassurance
- Menstrual diary
- Nonsteroidal anti-inflammatory drugs at menses

that can be managed by antiemetics. Intravenous therapy is usually continued until bleeding has ceased, in most cases within 24 hours. In patients with severe bleeding, some continuation of therapy is usually recommended. Oral equine estrogens (Premarin) in doses of 2.5 mg can be continued for an additional 20 to 25 days. Medroxyprogesterone acetate (10 mg) can be added for the last 7 to 10 days which allows for a withdrawal menses after therapy. Alternatively, patients can be started on a combination oral contraceptive cycle following intravenous therapy. Young women with known bleeding disorders may need adjunctive therapy, in the form of desmopressin acetate or antifibinolytics, in addition to hormonal therapy [8].

If the bleeding is not associated with severe symptoms, but is interfering with daily activities, or if mild anemia is present, then consideration of hormonal treatment for cycle control is indicated. If the bleeding has been prolonged, the endometrium may be disordered and denuded in portions. For those adolescents, administration of either oral equine estrogen (2.5 mg for 21–25 days followed by 10 mg medroxyprogesterone acetate for the last 7 days) or a combination oral contraceptive in an accelerated dosing is appropriate. Pills may be given two times daily for 1 week, followed by 3 weeks' of regular dosing of low-dose, combined

oral contraceptives [29]. For subsequent cycle control, cyclic oral medroxyprogesterone acetate, norethindrone acetate, or combination, low-dose oral contraceptives may be prescribed. Cyclic oral progesterone is administered for 10 days each month to prevent the actions of unopposed estrogen and stabilize the endometrium [8]. Withdrawal of progesterone each month allows organized sloughing of the endometrium and clinically leads to predictable menses during the perimenarchal, anovulatory period. Although oral progesterone that is administered in this fashion is effective and has minimal side effects, it is not appropriate in all adolescents. Some adolescents who take progestins experience side effects, such as bloating, increased acne, and increased appetite. Cyclic progestins do not offer protection against pregnancy and require intermittent monthly compliance, which may be difficult for some. Combination, low-dose, oral contraceptives offer another alternative. Davis et al [30] found that triphasic norgestimate-ethinyl estradiol was significantly more effective than placebo in improving abnormal bleeding patterns; 80% of women showed improvement [30]. Oral contraceptives offer reliable menstrual periods for adolescents with troublesome bleeding with a low incidence of complications and many noncontraceptive benefits. In hyperandrogenic adolescents, oral contraceptives are particularly beneficial in the improvement of acne and control of hirsutism. Compliance and problems with breakthrough bleeding on the low-dose regimens remain challenges of administration, which require more frequent visits and provider time. In healthy adolescents with no contraceptive needs, therapy is recommended for 3 to 6 months. Patients should then be encouraged to keep a close menstrual diary and return at frequent intervals to ensure that further therapy is not warranted.

For many adolescents with only mild symptoms of menstrual irregularity or prolonged menses, reassurance and education about the normal menstrual cycle will be sufficient therapy. Menstrual calendars can help the adolescent to visualize the cyclic changes of her menses and anticipate her bleeding. Parameters of acceptable bleeding can be established early so she can get access to help easily if her menstrual cycles deteriorate.

For adolescents with complaints of heavy, prolonged menses, the addition of nonsteroidal anti-inflammatory drugs may offer improvement in symptoms. Naproxen sodium and mefenamic acid are associated with a 46% and 47% decrease in blood loss at the time of menses, respectively [31]. Nonsteroidal medications have a direct endometrial effect on the balance between thromboxane A2, a potent vasoconstrictor, and PGI_2, a vasodilator, that leads to decreased menstrual flow [32]. Medication should be started at the onset of the menstrual flow and continued through the heavy days of bleeding. Antifibrinolytics, such as transexamic acid and aminocaproic acid, are very effective in decreasing blood loss, but the side effects of nausea, vomiting, headaches, and abdominal pain limit their usefulness in adolescents [8].

Depomedroxyprogesterone acetate has gained popularity as an effective contraceptive agent for adolescents, but does not have a significant place in the management of their abnormal bleeding. Although it may induce the desirable side effect of amenorrhea in some patients, it is associated with prolonged

breakthrough bleeding and other undesirable side effects, such as weight gain, hair loss, depression, and perhaps decreased bone mineral density among some groups [33]. It can produce protracted suppression of ovulation and thus delay the effect of the maturation of the HPO axis after administration is terminated. Other therapies that are sometimes mentioned with adults, including the use of GnRH agonists with add-back therapy and levonorgesterel impregnated IUDs, have little place in the management of adolescent, menstrual dysfunction. Surgical management, such as dilation and curettage or hysteroscopy, has limited usefulness in the management of adolescent patients.

Prognosis

Irregular, unpredictable, or heavy bleeding in adolescents usually occurrs as a result of a lack of full maturation of the HPO axis. Over the first 3 to 5 postmenarchal years, most patients will develop regular, cyclic menses. Southam and Richart [34] found that if normal menses had not developed within 4 years of menarche, the chance for normal menstrual function was low. Many of these women had decreased reproductive potential, endometrial cancer, and subsequent gynecologic surgeries that suggested that an underlying disease process contributed to their bleeding dysfunction.

Summary

Abnormal and irregular bleeding are extremely common in the adolescent period and can be looked upon as a part of normal reproductive development. It is essential to have a firm grasp on the normal, physiologic development of the menstrual cycle. Prompt recognition and treatment of the situations that may indicate underlying disorders or diseases is possible. It is important to recognize the distinct needs, goals, and developmental stages of adolescent patients. No single therapy or approach is universal in the diagnosis and treatment, but must be tailored to the needs of the individual adolescent and her situation.

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Treatment of the adolescent patient with polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) affects 5% to 10% of reproductive-aged women [1]. Frequently, PCOS is defined as a syndrome of ovarian hyperandrogenism and chronic anovulation in women without an underlying adrenal or pituitary cause [2]. Diagnosis of this condition requires evidence of menstrual dysfunction (oligomenorrhea or amenorrhea) and either clinical or biochemical evidence of hyperandrogenism. Although earlier descriptions of PCOS included polycystic ovarian morphology on ultrasound, this finding is no longer considered essential for its diagnosis. Many women with PCOS have the onset of symptoms during adolescence [3]; therefore, it is essential that health care providers for adolescents be familiar with the evaluation and treatment of this disorder.

Pathophysiology

The etiology of PCOS remains unknown and is an area of active investigation. Theories have focused on the impact of luteinizing hormone (LH) stimulation of the ovary and, more recently, on the role of insulin in causing ovarian hyperandrogenism.

Neuroendocrine abnormalities

Luteinizing hormone pulse frequency and amplitude are increased in women with PCOS, suggesting an aberrant pattern of hypothalamic gonadotropin-releas-

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ing hormone (GnRH) secretion as a causative mechanism in this disorder [4,5]. Adolescent females with PCOS also exhibit similar elevations in LH pulse amplitude and frequency [6,7]. LH levels remain tonically elevated for the duration of the menstrual cycle [8], thereby stimulating androgen secretion by ovarian theca cells. Ovarian steroidogenesis remains intact [9].

Ovarian androgen excess and relatively diminished levels of estrogen may impair follicular development, resulting in anovulation [10]. In addition, low-normal follicle-stimulating hormone (FSH) levels result in less efficient aromatization of androgens to estrogens, thereby producing an environment of more androgens than estrogens. Estrones produced from peripheral conversion of androgens are also thought to sensitize gonadotrophs to secrete LH, which then initiates or maintains ovarian androgen secretion [11]. Low-normal FSH levels may contribute to normal or elevated levels of inhibin that have been reported in women with PCOS [12].

Insulin resistance

Insulin resistance is broadly defined as a state in which a greater than normal amount of insulin is required to elicit a quantitatively normal response. Barbieri et al have suggested that insulin resistance has a role in the development of PCOS [13]. Women with PCOS have decreased sensitivity to insulin in muscle and adipose tissue (although not in the liver), leading to a compensatory increase in levels of insulin. Decreased insulin sensitivity is demonstrated in lean and obese women, suggesting the defect is intrinsic to PCOS [14]. Insulin sensitivity is decreased by 50% in adolescents with PCOS [6]. Unlike in adults with PCOS, insulin resistance in obese adolescents with PCOS seems to be compensated by increased pancreatic production of insulin [15]. Prepubertal girls with premature adrenarche and acanthosis nigricans have decreased insulin sensitivity [16].

Insulin resistance in PCOS seems to be caused by a postbinding defect in insulin receptor signaling [17]. One proposed mechanism includes serine phosphorylation of the insulin receptor that inhibits its signaling [1]. This defect has been demonstrated in approximately 50% of women with PCOS [18]. In addition, serine phosphorylation of cytochrome P450c17α stimulates ovarian androgen production, providing a possible explanation for abnormal peripheral insulin action and preservation of action at the ovary [19]. Another proposed mechanism of insulin resistance is a deficiency of d-*chiro*-inositol phosphoglycan, a mediator of insulin action [20].

High levels of insulin are thought to stimulate ovarian androgen production through the insulin and insulin-like growth factor (IGF) receptor by a number of mechanisms. Insulin directly stimulates ovarian androgen production from the ovarian stroma [21]. High levels of insulin have been shown to inhibit hepatic production of IGF-1 binding protein, resulting in higher levels of IGF-1. Insulin may then bind to the IGF-1 receptor to increase ovarian steroidogenesis [22].

Clinical presentation

Studies of the clinical manifestations of PCOS in the adolescent are sparse. PCOS is a heterogeneous disorder, and patients can present with a wide range of symptoms and laboratory abnormalities. Typical clinical findings are associated with hyperandrogenism and anovulation.

Hirsutism and acne are the most common manifestations of hyperandrogenism in PCOS and can be a cause of embarrassment among female adolescents. Hirsutism is defined as the growth of pigmented coarse hair in androgen-dependent areas such as the face, chest, back, and lower abdomen. The distribution and severity of the hirsutism can be quantified using the Ferriman and Gallwey score, with a score of 8 or greater signifying significant hair growth [23]. Ethnic and racial differences exist in body hair type and distribution and should be taken into consideration when assessing hirsutism. The leading cause of hirsutism in adolescence is PCOS [24]. Premature adrenarche and hirsutism that occur before puberty also have been associated with PCOS in adolescents [16,25]. Another sign of androgen excess, acne, is common in adolescents with PCOS. More than one third of women presenting to a dermatology clinic with acne are diagnosed with PCOS [26].

Menstrual irregularity is a significant component of PCOS. Secondary amenorrhea, oligomenorrhea, and dysfunctional uterine bleeding are some of the menstrual irregularities seen with anovulation. Menarche typically begins at a normal age but can be delayed in girls with PCOS. Irregular menses, most commonly oligomenorrhea, persisting from the time of menarche well into adolescence is a common feature of adolescent PCOS [27,28]. Because menstrual irregularities are commonly seen in adolescents, it may be difficult to make the diagnosis of PCOS unless there are concomitant signs of hyperandrogenism.

Obesity is often associated with PCOS. Nearly 50% of hyperandrogenic anovulatory women are obese. The weight distribution is centripetal, with increased waist-to-hip ratios of greater than 0.85. A study of adolescents with PCOS in Singapore revealed a 27% incidence of obesity (defined as weight > 120% of ideal body weight), with 9% of the population being thin (weight < 85% of ideal body weight) [29].

Acanthosis nigricans is a raised, velvety, hyperpigmentation of the skin seen in the axilla, neck, and intertrigenous areas. It is a marker of insulin resistance. Prepubertal girls with acanthosis nigricans and premature adrenarche have significantly decreased insulin sensitivity when compared with prepubertal girls without acanthosis nigricans [16].

Polycystic-appearing ovaries on ultrasound, defined as more than 10 follicles 2 to 8 mm in diameter located peripherally on the ovary, are commonly seen in patients with PCOS. van Hooff and colleagues found the incidence of polycystic-appearing ovaries to be 45% in oligomenorrheic girls compared with a 9% incidence in normally menstruating adolescents [30]. Nevertheless, polycystic ovaries also can be seen in 33% of normally menstruating adolescents [27] and prepubertal girls [31], and in other conditions, such as congenital adrenal hyper-

plasia, hypothalamic amenorrhea, and hyperprolactinemia [32]. Because polycystic ovarian morphology can be seen in a variety of pathologic conditions as well as in normal individuals, ultrasound is not useful in the diagnosis of PCOS.

As is true in adults, adolescents with PCOS exhibit elevated LH pulse amplitude and frequency, an increased LH-to-FSH ratio, and elevated androgens [6]. Although elevated free or total testosterone levels are biochemical confirmations of hyperandrogenism, it is not uncommon to find minimally elevated or even normal androgen levels in adolescents with clinical signs of PCOS [33]. Approximately 50% to 60% of women with PCOS have elevated levels of dehydroepiandrosterone sulfate [34]. Some investigators stress the clinical diagnosis of PCOS and suggest minimal reliance on biochemical testing [35].

Insulin resistance also has been described in adolescents with premature adrenarche [36]. Some investigators suggest that premature adrenarche may be a precursor of PCOS [36,37]. Insulin sensitivity, seen with increased fasting insulin levels, has been reported in obese adolescents with clinical signs of hyperandrogenism; an increased insulin response is seen with glucose intake or meals [6]. Type 2 diabetes mellitus can also present in adolescents with obesity, acanthosis nigricans, or premature adrenarche [38].

Evaluation

The laboratory evaluation of an adolescent with suspected PCOS varies with the symptoms and clinical findings. To establish the diagnosis of PCOS, the goals are to confirm ovarian hyperandrogenism and exclude other causes of hyperandrogenism and menstrual dysfunction, such as adrenal or ovarian tumors, nonclassical adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, and thyroid disease.

Physical examination is essential in evaluating for the presence of PCOS. Measurement of weight and the waist-to-hip ratio, and an assessment for clinical signs of hyperandrogenism (including hirsutism, acne, or signs of virilization) and insulin resistance (acanthosis nigricans) can be helpful in establishing the diagnosis of PCOS. One should evaluate for clinical signs of other causative disorders to exclude their diagnoses.

Hormone assays for free and total testosterone and dehydroepiandrosterone (DHEA) are commonly performed to confirm the diagnosis of PCOS and to exclude other causes of hyperandrogenism. Total testosterone levels greater than 200 ng/dL in the setting of rapid progression of hirsutism and the presence of virilization are consistent with an androgen-producing ovarian tumor. DHEA levels greater than 7000 ng/dL are indicative of an adrenal tumor. The diagnosis of most tumors can be based on history and physical findings as opposed to biochemical levels [33]. Nonclassical adrenal hyperplasia can be excluded by obtaining a basal 17-hydroxyprogesterone level during the follicular phase of the cycle (or at any time in an anovulatory patient). An adrenocorticotropic hormone

stimulation test should be performed if an elevated 17-hydroxyprogesterone level is found (>2 ng/mL) [39].

Assays for prolactin and thyroid-stimulating hormone are recommended to exclude the diagnoses of hyperprolactinemia and hypothyroidism, both of which can present with menstrual irregularities and anovulation. LH-to-FSH ratios are not useful in the diagnosis of PCOS given that as many as 40% of women with PCOS have normal ratios [33]. Determination of FSH levels may be required to exclude the diagnosis of premature ovarian failure in adolescents with primary or secondary amenorrhea without signs of hyperandrogenism.

Screening for diabetes mellitus should be performed in all patients with PCOS owing to the risk for glucose intolerance and diabetes in this population. A fasting glucose level should be obtained in all adolescents with PCOS. A 2-hour, 75-g oral glucose tolerance test (OGTT) is more sensitive for diagnosing impaired glucose tolerance [40]. The OGTT may be prudent in high-risk adolescents, because the results from the recent diabetes prevention trial have shown that treatment of impaired glucose tolerance decreases the risk for diabetes [41]. Evaluating for insulin resistance is not mandatory but may be helpful in directing therapy. Adolescents with obesity and acanthosis nigricans should be screened for insulin resistance. A fasting glucose-to-insulin ratio of less than 4.5 has been shown to indicate insulin resistance in women with PCOS [42]. This ratio may also help identify adolescents at risk for type 2 diabetes mellitus [15].

As discussed earlier, ultrasound findings are not useful in the diagnosis of PCOS [32]. If one is unable to perform an adequate pelvic examination to rule out ovarian pathology, or if an ovarian tumor is suspected, an ultrasound evaluation is warranted.

Health consequences

Long-term health consequences of PCOS include an increased risk for obesity, diabetes mellitus, heart disease, dyslipidemia, hypertension, endometrial hyperplasia, and infertility.

Obesity is associated with many health problems. Fifty percent to 60% of women with PCOS are obese. A waist-to-hip ratio greater than 0.85 is associated with an increased risk for myocardial infarction. In addition, an elevated waist-to-hip ratio is associated with increased basal insulin concentrations, an increased incidence of diabetes mellitus, and an increased incidence of hypertension [43].

The prevalence of impaired glucose tolerance and non–insulin-dependent diabetes mellitus is substantially higher in women with PCOS when compared with weight- and age-matched controls. Two large studies of patients with PCOS, defined as oligomenorrhea and hyperandrogenism, found the prevalence of impaired glucose tolerance and diabetes mellitus to be 31% to 35% and 7.5% to 10%, respectively [40,44]. In controls, the prevalence of impaired glucose

tolerance and diabetes mellitus was 14% and 0%, respectively [40]. The mean age of the patients in these studies was 25 to 30 years, suggesting an earlier age of onset for these conditions in the PCOS population. An abnormal fasting glucose, the presence of PCOS, an elevated waist-to-hip ratio, and increased body mass index are associated with abnormal postglucose challenge tests [44]. Type 2 diabetes has been documented in adolescents with obesity, acanthosis nigricans, or premature adrenarche [38].

When compared with controls, women with PCOS have a higher prevalence of coronary heart disease and cerebrovascular disease, diabetes mellitus, hypertension, and obesity, and are more likely to have a family history significant for coronary heart disease or diabetes mellitus [45]. PCOS is also associated with more severe coronary disease [46]. Women with PCOS have higher total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and lower high-density lipoprotein cholesterol levels [47,48]. Although PCOS is associated with cardiovascular risk factors, a large retrospective study of women with PCOS did not find a higher than average mortality from circulatory disease [49]. Further research is needed to clarify this issue.

Treatment

In treating the adolescent with PCOS, short- and long-term goals of therapy should be considered. Short-term goals include the regulation of menses, the control of hirsutism and acne, and the stabilization or reduction of weight. Long-term goals are less pressing to the adolescent and include the prevention of diabetes, endometrial hyperplasia, obesity, heart disease, and infertility. Multiple concomitant therapies are often necessary to address the variety of symptoms, but they also confer an additive benefit with regard to the efficacy of treatment. Traditional treatment of PCOS has focused on the suppression of symptoms of androgen excess and anovulation. Newer therapies with insulin-sensitizing agents are intended to correct the underlying metabolic disorder. Currently, no studies have compared the effectiveness of these two approaches. Randomized controlled trials are needed to determine whether insulin-sensitizing drugs are better than traditional therapies and, if so, to determine which patients would benefit from these medications.

Menstrual irregularity

Regulation of menses is important, because the anovulation seen in PCOS is associated with the development of endometrial hyperplasia and carcinoma. In addition, irregular menses and abnormal bleeding can be troublesome for the adolescent.

Cyclic progestin and oral contraceptives (either combined or progestin-only formulations) can be used to resume menstrual regularity. In contrast to oral contraceptives, cyclic progestins do not suppress ovarian androgen production. Depo-

medroxyprogesterone acetate (Depo-Provera) is an injectable alternative to oral contraceptives that can effectively decrease ovarian activity. Ovarian suppression with Depo-Provera is much greater than that achieved with oral contraceptives.

Hirsutism and acne

Hirsutism and acne are difficult problems for an adolescent, because they have a significant effect on image and self-esteem. One should address these concerns even if symptoms are mild. The goals of hirsutism therapy are to control current hair growth and to prevent growth of new hair. Once hair is present, it is hard to remove; therefore, therapy should be initiated early when the adolescent is beginning to have symptoms rather than waiting until hair growth is significant. The risks and benefits of starting therapy in a young adolescent must be weighed carefully with this goal in mind.

Drug therapy for hirsutism is directed toward decreasing the production of androgens, blocking the action of androgens at the receptor, and slowing hair growth. Combining mechanical hair removal techniques with drug therapy achieves the best results. Because the growth cycle of hair is relatively long, especially for hair on the face, the results of treatment may not be observed for as long as 6 months. The adolescent should be counseled about realistic expectations of therapy to encourage compliance and avoid disappointment.

Acne is a common problem among adolescents with PCOS. As is true for hirsutism, treatment should include drug therapy to reduce circulating androgens and to decrease their effect on the pilosebaceous unit. Consultation with a dermatologist is advised for nonhormonal treatments such as antibiotics, benzoyl peroxide, and 13-*cis*-retinoic acid.

Mechanical hair removal and topical techniques

Mechanical hair removal is the only way to get rid of existing hair. Mechanical removal of unwanted pigmented hair can be accomplished by several techniques, including plucking, waxing, shaving, and depilatory use. Shaving is the preferred technique, because it is less traumatic than the other methods, which may induce folliculitis and ingrown hairs. Although shaving does result in a ''stubblelike'' feel, it does not lead to worsening of hirsutism. Depilatories can lead to skin irritation, especially on the face. Electrolysis is very successful in the treatment of hirsutism and has the advantage of permanent removal of the hair follicle. This technique can be expensive, tedious, highly operator dependent, and not applicable for large areas of the body. Laser treatment of hirsutism is a newer technique for long-term hair removal that has the advantage of covering large areas.

Eflornithine HCl, a topical cream, has been developed for the treatment of hirsutism. It is an irreversible inhibitor of ornithine decarboxylase, an enzyme that stimulates hair growth. Clinical studies of eflornithine HCl show a reduction in the rate of hair growth with its use [50]. Side effects include burning, stinging, and tingling. This medicine has not been tested in the adolescent population.

Combination oral contraceptives

The combined oral contraceptive pill effectively controls symptoms of PCOS. Oral contraceptives regulate menstruation and prevent endometrial hyperplasia. They are also effective in the treatment of hirsutism and acne [51] by suppressing FSH and LH, which decreases ovarian androgen production [52], and by increasing the hepatic production of sex hormone–binding globulin, which decreases circulating free androgens [53]. There is no significant difference in clinical efficacy among oral contraceptives despite inherent differences in progestin androgenicity [54,55]. Low-dose oral contraceptives containing 20 μg of ethinyl estradiol have been shown to be effective in the management of acne [56].

Antiandrogen therapy

The rationale for using antiandrogen therapy is to block the action of androgens. These therapies block androgen binding to the androgen receptor or inhibit 5α-reductase, the enzyme that converts testosterone to the active androgen, dihydrotestosterone, at the level of the hair follicle. Several antiandrogen medications are available, including spironolactone, flutamide, finasteride, and cyproterone acetate (not available in the United States). Antiandrogens are potentially teratogenic and should not be used without contraception in women at risk of becoming pregnant. None of these medications are approved by the US Food and Drug Administration (FDA) for the treatment of hirsutism. Antiandrogens are frequently used in combination with oral contraceptives, because their mechanism of action is different, and their combined effect is additive [57,58]. In addition, oral contraceptives have the added benefit of preventing side effects of irregular bleeding seen with antiandrogens.

The most commonly used antiandrogen is spironolactone, an aldosterone antagonist that was originally developed to treat hypertension but found to be more effective as an antiandrogen. Its mechanisms of action include competitive binding at the androgen receptor and inhibition of testosterone biosynthesis. Effective doses used to treat hirsutism are 25 to 100 mg twice daily. This effect is dose dependent [59], with a 30% to 40% decrease in hirsutism score achieved with 50 mg twice daily [57,60]. Therapy with spironolactone should be initiated with a dose of 25 mg daily and increased in a progressive fashion over several weeks to avoid side effects. Side effects are mild and can include menstrual irregularity, hypotension, lethargy, urinary frequency, and hyperkalemia. One-time monitoring of potassium is suggested following the initiation of therapy.

Flutamide is an antiandrogen used in the treatment of prostate cancer. Its mechanisms of action in treating hirsutism include blocking the androgen receptor and decreasing adrenal 17,20-lyase activity, resulting in reduced adrenal androgens. The effective dose is 250 to 500 mg/day, although one study found no difference in efficacy when these doses were compared [61]. Side effects include dry skin, decreased libido, increased appetite, and amenorrhea. Drug-induced fatal hepatotoxicity has been reported, occurring in less than 0.5% of patients [62]. In a small uncontrolled study, Ibanez et al evaluated 18 girls aged 14 to 18 years who were treated with flutamide, 250 mg daily, for 18 months [63]. Following

treatment, a decrease in the mean Ferriman and Gallwey score from 15 to 8 ($P < 0.001$) and a decrease in the free androgen index ($P < 0.01$) were observed. No significant side effects were reported.

Finasteride is a 5α-reductase inhibitor used in the treatment of benign prostatic hypertrophy and hair loss in men. Finasteride selectively inhibits type 2 5α-reductase, the form of the enzyme predominating in the hair follicle. The recommended dose is 5 mg daily. The drug is well tolerated with few side effects in women. The risk of teratogenicity with finasteride is a concern, because type 2 5α-reductase is responsible for the development of male external genitalia; in utero exposure to finasteride can result in ambiguous genitalia in the male fetus.

Cyproterone acetate is a potent progestin that exhibits antiandrogen activity [64] and suppresses ovarian androgens. Cyproterone acetate is available in combination with ethinyl estradiol as the oral contraceptive Diane (cyproterone acetate, 2 mg; ethinyl estradiol, 35 μg). Treatment with Diane results in a significant decrease in hirsutism scores over 6 months [58]. Cyproterone acetate is not available in the United States.

All antiandrogens are effective in the treatment of hirsutism. Moghetti et al compared the effects of spironolactone, 100 mg/day, flutamide, 250 mg/day, and finasteride, 5 mg/day with placebo in 40 hirsute women over a period of 6 months [60]. No significant difference in improvement was seen in any treatment group, and all of the medications achieved a 30% to 40% improvement in Ferriman and Gallwey hirsutism scores. Another study found flutamide to be more effective than finasteride [65]. In the United States, spironolactone is the most widely used antiandrogen owing to its lower cost, effectiveness, and side-effect profile.

Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists can be used in the treatment of hirsutism in patients with PCOS. The rationale behind their use is complete suppression of the ovary, resulting in decreased androgen levels. Hirsute women treated with GnRH agonists show improvements in hirsutism scores and androgen levels [66,67]. Concomitant add-back therapy with oral contraceptives has been shown to be more effective than GnRH agonist treatment alone [67]. A GnRH agonist combined with estrogen is more effective than an oral contraceptive alone in the treatment of hirsutism [68]. Adding an oral contraceptive to a GnRH agonist not only decreases free androgens by increasing sex hormone–binding globulin but also corrects the hypoestrogenism caused by the agonist. This combined regimen can be used long-term in patients with severe symptoms; however, it should not be used routinely because of its expense and concerns regarding the effect on peak bone density in adolescents.

Obesity

In addition to improving appearance, weight loss can significantly benefit patients with PCOS by improving peripheral estrogen and ovarian androgen production. Weight loss has been shown to be effective in decreasing androgen

levels and resuming menstruation. A 7% decrease in body weight has been shown to decrease testosterone levels and lead to resumption of menses. Lifestyle modifications, including the restriction of calories and the performance of exercise, can decrease waist circumference and improve insulin sensitivity and fasting insulin levels in anovulatory women with PCOS [69]. Clark et al reported that an intensive program of calorie restriction, exercise, and lifestyle modification over 6 months resulted in ovulatory cycles in 90% of patients [70]. The average decrease in body mass index was -3.7 kg/m^2, and the average weight loss was 10.2 kg. Similarly, a study of 13 obese women with PCOS using diet, exercise, and lifestyle modification over 6 months showed a mean weight loss of 11.55% and a significant improvement in insulin sensitivity [71]. First-line therapy for PCOS in the obese adolescent should include counseling regarding the importance of diet and exercise in the management of this disorder. Emphasis should be placed on healthy eating habits and exercise rather than rapid weight loss. A nutritionist can be helpful. In this manner, the symptoms of PCOS will improve, and the consequences of obesity may be avoided.

Insulin-sensitizing agents

With emerging evidence suggesting that insulin resistance has a significant role in the pathophysiology of PCOS, insulin-sensitizing agents have been proposed as treatment for this disorder. Although most current regimens treat the symptoms of PCOS, insulin-sensitizing agents are intended to correct the underlying metabolic defect of this syndrome, potentially conferring a treatment advantage. The classes of agents that have been investigated include the biguanides, thiazolidinediones, and d-*chiro*-inositol. These drugs are not approved by the FDA for this indication. Although insulin-sensitizing drugs show great promise in the treatment of PCOS, long-term randomized controlled studies are needed before they can be recommended as first-line therapy in adolescents.

Metformin

The biguanide metformin inhibits hepatic glucose production and increases peripheral tissue sensitivity to insulin [72]. In doses of 1500 to 2000 mg per day, metformin has been shown to decrease androgens, decrease insulin, improve ovulatory rates, and lead to resumed menstrual cyclicity [73–75]. Most studies have involved a small number of select patients, are observational in design, and are of short duration (12–26 weeks). The effect of metformin on hirsutism has not been studied adequately. One long-term study showed no improvement in hirsutism scores with metformin therapy [74], whereas another showed a significant improvement in a small number of adolescents [63].

Few studies have evaluated the use of metformin in adolescents; however, its use seems safe in small observational pilot studies. Glueck et al evaluated metformin therapy administered in combination with a high-protein, low-carbohydrate diet for 6 months in 11 adolescent girls with PCOS [76]. Menstrual cyclicity resumed in 91% of girls, and 9 of 11 girls lost weight. Ibanez et al studied

10 nonobese adolescent girls using metformin for 6 months and found resumption of regular menses in all subjects, as well as a decrease in hirsutism, testosterone levels, and the free androgen index [77]. Furthermore, metformin therapy in 18 nonobese adolescents with PCOS resulted in ovulation in 78% of subjects [77].

Treatment with metformin has been compared with the oral contraceptive containing cyproterone acetate in obese women with PCOS [78]. Both therapies decreased serum testosterone levels following 6 months of treatment. In addition, metformin resulted in improved menstrual cyclicity and a significant decrease in the waist-to-hip ratio and insulin concentrations, whereas the oral contraceptive resulted in significant improvement in hirsutism.

Weight loss in women with PCOS is difficult. Although a small decrease in weight has been reported [79,80] with metformin, the drug does not reliably lead to weight loss in patients with PCOS [74,81,82]. When metformin therapy is combined with a restricted calorie diet, significant weight loss is observed [76,83]. The improvement in metabolic parameters seen with metformin is independent of weight loss [79,81,84].

Even though metformin decreases the risk of type 2 diabetes mellitus in individuals with glucose intolerance [41], it is not known whether it decreases the risk of diabetes in individuals with PCOS. Further studies are needed to determine the long-term benefits of this therapy.

Thiazolidinediones

Many studies have evaluated the effectiveness of the thiazolidinedione troglitazone on parameters of hyperandrogenism and anovulation [85,86]. When compared with a placebo, troglitazone decreases free testosterone and fasting insulin levels and improves ovulation rates with increasing doses [85]. Troglitazone has been taken off the market owing to liver toxicity. Newer thiazolidinediones, such as pioglitazone and rosiglitazone, are not toxic to the liver. Further research is needed to prove their safety and efficacy in patients with PCOS.

D-chiro-inositol

Deficiency of a second messenger, inositol phosphoglycan, has been observed in patients with impaired glucose tolerance [56] and type 2 diabetes mellitus [87]. Its replacement by oral administration of d-*chiro*-inositol to women with PCOS has been shown to improve glucose tolerance [20]. In addition, many women treated with d-*chiro*-inositol have a marked improvement in ovulatory function when compared with a placebo (86% versus 27%), as well as improvements in blood pressure and plasma triglyceride concentrations [20]. This drug is being evaluated in phase II and III clinical trials.

Summary

Frequently, a multidisciplinary approach is needed in the management of the adolescent with PCOS. Treatment must be provided in a supportive environment.

Because adolescent females are concerned about their appearance and body image, short-term treatment goals are usually directed toward the amelioration of hirsutism, acne, and irregular menstruation. Although not immediately concerning to the adolescent, the prevention of long-term sequelae from anovulation and hyperinsulinemia is also important. Multiple concomitant therapies are often necessary to address the variety of symptoms and achieve better results. Recent studies have investigated the role of the insulin-sensitizing agent, metformin, in the treatment of PCOS. Although most studies show a benefit, the conclusions are limited owing to the small numbers of select patients, observational designs, and short durations of follow-up. In addition, there are few data comparing insulin-sensitizing drugs with traditional therapies for PCOS. More long-term, randomized controlled trials are needed to determine the utility of insulin-sensitizing agents, their long-term benefits, and the ideal patient population for their use.

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Eating disorders

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Frequently, gynecologists and primary care clinicians are the first medical providers to recognize and begin management of eating disorders in girls and young women. Anorexia nervosa, bulimia nervosa, and the newest category, eating disorder not otherwise specified, remain a significant cause of morbidity and mortality in these groups. Early detection and initial management may help to prevent progression to a debilitating or chronic state, including the potential for permanent loss of bone if the behaviors are uncorrected. The gynecologist, reproductive endocrinologist, or adolescent medicine specialist may see referrals for amenorrhea. These visits may serve as a diagnostic entry point for many patients with unrecognized eating disorders. Management of eating disorders typically requires a multidisciplinary team approach, often spearheaded by the clinician initially detecting the illness. This article addresses the definitions and prevalence of eating disorders, tips on recognition and management of medical complications, and reproductive health concerns for these young women. Issues surrounding care of the patient with the female athlete triad, or amenorrhea, osteopenia, and eating disorders, are also discussed.

Definitions and prevalence of eating disorders

Described as the ''relentless pursuit of thinness'' [1], anorexia nervosa is characterized by extreme weight loss or failure to gain weight during childhood along expected parameters, a distorted body image, and an overwhelming fear of obesity [2,3]. Bulimia nervosa, literally meaning ''appetite like a bull'' in its

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Greek derivation, is defined by binges or large consumptions of food occurring at least twice weekly for at least 3 months, with attempts at compensation for the binges by means of vomiting, laxative abuse, hyperexercising, or other purging behavior. Bulimic individuals may be of normal weight or overweight for height. Although individuals with anorexia nervosa may be in complete denial of the existence of any problem caused by their low weight or ongoing weight loss, patients with bulimia nervosa may find their behavior distressing or egodystonic.

Table 1
Diagnostic criteria for eating disorders

Anorexia nervosa
1. Intense fear of becoming fat or gaining weight, even though underweight
2. Refusal to maintain body weight at or above a minimally normal weight for age and height (ie, weight loss leading to maintenance of body weight <85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight <85% of that expected)
3. Disturbed body image, undue influence of shape or weight on self-evaluation, or denial of the seriousness of the current low body weight
4. Amenorrhea or absence of at least three consecutive menstrual cycles (persons with periods only inducible after estrogen therapy are considered amenorrheic)

Types
- Restricting—no regular bingeing or purging (self-induced vomiting or use of laxatives and diuretics)
- Binge eating/purging—regularly binging and purging in a patient who also meets the above criteria for anorexia nervosa, also called "bulimic anorexia nervosa" or "bulimarexia"

Bulimia nervosa ("appetite of a bull")
1. Recurrent episodes of binge eating, characterized by
   a. Eating a substantially larger amount of food in a discrete period of time (ie, in 2 hours) than would be eaten by most people in similar circumstances during that same time period
   b. A sense of lack of control over eating during the binge
2. Recurrent inappropriate compensatory behavior in an attempt to prevent weight gain, such as self-induced vomiting, use of laxatives, diuretics, fasting, or hyperexercising
3. Binges or inappropriate compensatory behaviors occurring, on average, at least twice weekly for at least 3 months
4. Self-evaluation unduly influenced by body shape or weight
5. Disturbance not occuring exclusively during episodes of anorexia nervosa

Types
- Purging—regularly engages in self-induced vomiting or use of laxatives/diuretics
- Nonpurging—uses other inappropriate compensatory behaviors, such as fasting, hyperexercising, without regular use of vomiting or medications to purge

Eating disorder not otherwise specified (persons who do not meet criteria for anorexia nervosa or bulemia nervosa)
1. All criteria for anorexia nervosa except has regular menses
2. All criteria for anorexia nervosa except weight still in normal range
3. All criteria for bulimia nervosa except binges < twice a week or for < 3 months
4. A patients with normal body weight who regularly engages in inappropriate compensatory behavior after eating small amounts of food (ie, self-induced vomiting after eating two cookies)
5. A patient who repeatedly chews and spits out large amounts of food without swallowing
6. Binge eating disorder—recurrent binges but does not engage in the inappropriate compensatory behaviors of bulemia nervosa

Adapted from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Washington (DC): American Psychiatric Association; 1994. p. 539–50.

Binges or purges may occur in clandestine fashion, often accompanied by other impulsive behaviors, such as stealing food or money for food, alcohol abuse, or other problem behaviors [4].

The criteria for the diagnosis of eating disorders were revised in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition [5], in an attempt to facilitate early recognition and improve treatment (Table 1). Anorexia nervosa was further subclassified into two types: (1) restricting anorexia nervosa, occurring in persons who do not regularly purge, and (2) bulimic anorexia nervosa, occurring in persons who predominantly fast but who also purge by self-induced vomiting, diet pills, hyperexercising, or other techniques. The diagnosis ''eating disorder not otherwise specified'' allows a diagnostic code and description of patients who may not meet the criteria for anorexia nervosa or bulimia nervosa but who clearly manifest disordered eating. Examples include athletes who meet all of the criteria for anorexia nervosa but who have either not lost 15% of ideal body weight or are still menstruating. Signs and symptoms of anorexia nervosa and bulimia nervosa include the following:

Anorexia nervosa
Dry skin
Cold intolerance
Blue hands and feet
Constipation
Bloating
Lanugo hair
Scalp hair loss
Early satiety (delayed gastric emptying, slowed metabolism)
Weakness, fatigue, or low energy (despite high physical activity)
Short stature
Delayed puberty
Primary or secondary amenorrhea
Nerve compression (no padding)
Decreased bone density, easy fractures
Breast atrophy, atrophic vaginitis
Pitting edema of extremities
Cardiac murmurs (one third with mitral valve prolapse)
Fainting
Sinus bradycardia, orthostatic hypotension
Hypothermia

Bulimia nervosa
Mouth sores
Pharyngeal trauma
Dental caries
Heartburn, chest pain
Esophageal rupture

Muscle cramps
Weakness
Bloody diarrhea (in laxative abusers)
Bleeding or easy bruising (hypokalemia, platelet malfunction)
Irregular periods or amenorrhea
Fainting
Swollen parotid glands
Sinus bradycardia, orthostatic hypotension

Eating disorders can have an insidious onset. Typically, the individual who is either overweight or dissatisfied with current body image moves from a moderate effort to lose weight to intense preoccupation with weight loss and eating. Symptoms may not be obvious until a substantial amount of weight has been lost or unhealthy behaviors are firmly entrenched. The female athlete triad refers to the combination of amenorrhea, osteopenia, and eating disorders. An initial drive by the athlete to lose weight to improve performance is eventually replaced by a drive to lose weight as a goal in and of itself, regardless of negative impact on athletic performance.

Epidemiology of eating disorders

Incidence rates for anorexia nervosa have increased steadily from 1975 to 1995 in teenagers aged 10 to 19 years, whereas rates in adults have remained relatively constant [6–9]. Anorexia nervosa affects an estimated 1% of adolescent females, with 90% to 95% of all cases occurring in females; 1% to 5% of high school girls have bulimia nervosa, with the percentage as high as 19% in college women who are surveyed. The prevalence of eating disorder not otherwise specified is not well defined. Many of these patients have subclinical disease not captured well by epidemiologic data (eg, girls who have not lost a menstrual period or who otherwise look normal). Anecdotally, anorexia nervosa has been seen in patients as young as 6 years, with abnormal eating attitudes and behaviors found in school-aged children in grades three through six [10,11]. It is also an ''equal opportunity'' disease, with growing numbers of cases seen in minority populations in the United States [12–15] and in other countries not previously experiencing these problems [9,16,17]. When American television programs were viewed by the population of Figi in the past few years, a sudden surge in the prevalence of eating disorders was noted among the adolescent girls, who now attempt to emulate their western ''superpeers'' by attaining physiques not previously natural to their culture.

Using the modified Eating Attitudes Test [18,19], the rate of disordered eating was found to be as high as 17% among girls coming to a hospital-based reproductive endocrinology clinic compared with the finding of abnormal eating attitudes and behaviors in 7% of girls of the same age range presenting for health maintenance visits to the same institution [20]. The prevalence of eating disorders in female athletes has been estimated to range from 15% to 62% [21–25]. In a

survey of college gymnasts, Rosen et al found that 32% manifested at least one pathogenic practice for weight control, with unhealthy behaviors found in 74% of gymnasts, 50% of field hockey players, 47% of runners, and 25% of other female athletes involved in softball, track, tennis, and volleyball [24]. The vast majority (70%) believed that their behaviors were harmless. These behaviors included the use of diet pills or diuretics by 25%, binges more than twice per week by 20%, laxative abuse by 16%, and self-induced vomiting by 14%. Among a group of 93 elite women runners, 25% displayed binge eating, 13% had been diagnosed previously with anorexia nervosa, 9% binged and purged, and 34% had atypical eating practices [26]. In another study, Rosen and Hough found that 62% of college gymnasts reported unhealthy eating behaviors; two thirds of the athletes were told by their coaches that they were too heavy [23]. Athletes whose coaches had commented on their weights were more likely to engage in unhealthy dietary practices.

Unfortunately, abnormal eating attitudes and behaviors are often seen as the norm. Dummer et al studied the eating behaviors of 955 swimmers aged 9 to 18 years. Female athletes had more misconceptions about their weights than did male athletes. Overall, 80.5% of the athletes surveyed wanted to lose weight to look better, 58.5% to perform better, and 21.9% to improve their overall health [27]. Teenagers initiated pathogenic weight-control behaviors at young ages, including age 9 years for diet pills, age 10 years for fasting, age 11 years for vomiting, age 12 years for diuretics, and age 14 years for laxatives.

Evaluation of the individual with an eating disorder

The history should include questions on maximum weight and height and the time of their occurrence, minimum weight and height and the time of their occurrence, and the patient's ideal body weight. The degree of stress perceived with a missed workout can be a useful screening question, along with the intensity of exercise, hours per week, and level of competition. Other causes of stress should be elicited, along with questions on family structure and coping mechanisms, other risky behaviors, including cigarette, drug, and alcohol use and sexual activity, and the level of school and family functioning. Eating attitudes and behaviors should be ascertained, including weight loss methods and the use of dieting, vomiting, laxatives, diet pills, caffeine, and diuretics. A review of systems should include questions on headaches, galactorrhea, medications, and evidence of androgen excess. Other red flags useful in detecting an eating disorder include the following:

Suspicion of an eating disorder by anyone (parent, peer, teacher, primary care physician)
Isolation from friends
Frequent trips to the bathroom after meals
Recent change in dietary habits (new vegetarian)
Refusal to eat meals with family or friends
Change in bowel habits (constipation or diarrhea)

Constant dieting
Use of dietary aids or supplements to manipulate weight or appetite
Extra layering of clothes (too cold or just hiding)

The physical examination should include measurements of height, weight, orthostatic blood pressure, and pulse, along with a pelvic examination in patients who are sexually active. Estrogen status can be ascertained by physical examination, with evaluation of Tanner stage and breast atrophy, and by noting vaginal changes associated with estrogen effect as determined from a vaginal smear. A saline-moistened, cotton-tipped swab is rolled against the vaginal wall and then rubbed on a slide, with fixative applied. The percentage of superficial, intermediate, and parabasal cells is measured. One point is assigned for each superficial cell (more mature), with half a point for each intermediate cell, and 0 points for parabasal cells. A sum of over 40 implies some estrogen effect, with values of 50 to 60 seen in pubertal girls, 0 to 30 in prepubertal girls, and 31 to 55 in hypoestrogenic adults.

Primary and secondary amenorrhea should be evaluated in these young women. Teen-aged athletes may be engaging in other risky behaviors, and pregnancy must be excluded as a cause of amenorrhea. Other endocrine disorders may occur, including polycystic ovary syndrome, thyroid disease, or prolactinoma. Causes of hypergonadotropic hypogonadism (elevated follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) include ovarian failure (eg, Turner's syndrome, autoimmune ovarian failure). Hypogonadotropic hypogonadism can occur with chronic illnesses such as celiac disease or inflammatory bowel disease. Laboratory assessment for girls with amenorrhea and eating disorders is presented in Table 2.

Medical complications of eating disorders affect all organ systems and can include cardiac arrhythmias and sudden cardiac death, irreversible myocardial damage if ipecac (containing emetine) is used, fluid and electrolyte imbalances, dental erosions, esophagitis, slowed gastrointestinal motility with constipation

Table 2
Evaluation of the patient with an eating disorder

Screen for an eating disorder (can use the modified Eating Attitudes Test [19])
Check urine pregnancy test
Rule out other endocrine disorder by assaying FSH and LH
Normal—need further history
Low (hypogonadotropic hypogonadism)—consider stress, eating disorder, chronic illness
High (hypergonadotropic hypogonadism)—check chromosomes for Turner's syndrome/mosaic ovarian autoantibodies
Rule out endocrine disorder by obtaining thyroid stimulating and hormone level serum prolactin level
Serum electrolytes
CBC, erythrocyte sedimentation rate
Estrogen status (progestin withdrawal, serum estradiol or vaginal smear)
If delayed puberty, check wrist radiograph to differentiate bone age
If amenorrheic for 6–12 months, DEXA scan of spine or hip

Abbreviations: CBC, complete blood count; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

owing to delayed transit, leukopenia and pancytopenia, iron deficiency anemia, euthyroid sick syndrome, cortical atrophy, and changes in cerebral metabolism [28–32]. These complications can be broken down into effects of restricting, purging, binge eating, or any combination of these behaviors. For a full discussion of medical complications, the reader is referred elsewhere [29,30,33]. The discussion herein focuses mainly on issues of amenorrhea, osteopenia, and future fertility concerns.

Techniques for measurement of bone density

Currently, the most accurate and precise tool available to measure bone mineral density involves the use of dual-energy radiograph absorptiometry (DEXA). DEXA measures trabecular bone at the axial skeleton (eg, the lumbar vertebrae or femur) by using x-rays that emit two different energies to separate bone from surrounding soft tissue. The entire scan takes 10 to 15 minutes, with the amount of radiation at less than 5 mrem per scan, far less than the exposure from a chest radiograph (20 to 50 mrem) or full dental radiographs (300 mrem) [34]. In contrast, single-photon absorptiometry, used in Rigotti's study [35], measures only cortical bone. Quantitative CT of the spine measures only trabecular bone, involves 75 times the radiation exposure of absorptiometry, and should be avoided in girls and women of reproductive age [36]. DEXA scans should be performed on girls or women with eating disorders who have been amenorrheic for 6 months or longer and repeated yearly while they work on recovery.

Biochemical markers of bone turnover are available as a research tool but should not be used as a replacement of direct measurement of bone density (eg, DEXA) [37]. These markers include urinary measures of bone resorption (eg, collagen cross-links) and serum markers of bone formation (eg, osteocalcin, bone-specific alkaline phosphatase), all of which may be high in children and young adolescents in whom high turnover is expected as part of normal growth. In the patient with closed epiphyses, these markers can be used as an indirect measure of a patient's response to a specific therapy. For example, oral dehydroepiandrosterone (DHEA) given to young women with anorexia nervosa is associated with decreased urinary markers of bone resorption and increased serum markers of bone formation [38].

Menstrual cycles in athletes, girls, and women with eating disorders

Eumenorrheic or regular cycles are defined as regular flow occurring every 21 to 45 days, with 10 to 13 cycles per year. Oligomenorrhea refers to the occurrence of three to six cycles per year. Primary and secondary amenorrhea can occur in the context of eating disorders or intense athletics. Primary amenorrhea is defined as no menstrual periods by the age of 16 years. Secondary amenorrhea has been variably defined as the absence of periods for 3 months or the

occurrence of one period or less per year. In an attempt to standardize reporting, the international Olympic committee defined athletic amenorrhea as the occurrence of one or fewer periods per year [39]. The term *athletic amenorrhea* has been used to refer to a wide spectrum of reproductive system abnormalities, including altered pubertal progression, primary and secondary amenorrhea, abnormal luteal phase, anovulatory cycles, and oligomenorrhea [40]. The prevalence of these abnormalities ranges from 6% to 79% depending on the definitions of oligomenorrhea and amenorrhea used and the population surveyed with respect to age, nutritional status, years after menarche (postmenarchal age), sport, and level of activity [40]. The expected incidence of amenorrhea in adults is 2% to 5%; in contrast, the incidence of athletic amenorrhea has been reported to range from 3% to 66%, with disordered eating occurring in 15% to 62% of young female athletes [21,39,40–44].

Not all athletes have recognizable evidence of menstrual dysfunction. Luteal phase deficiency is defined as a shortening of the luteal phase with decreased levels of progesterone. The total cycle length can remain unchanged, leading to underdetection by the athlete. Luteal phase deficiency has been found in swimmers and runners and has been associated with infertility [45] and decreased bone density [46].

In 50% to 75% of normal-weight patients with bulimia nervosa, amenorrhea can precede weight loss [47]. Menstrual periods often cease after a 10% to 15% decrease in body weight [48]. The basic mechanism is thought to be an alteration in the regulation of gonadotropin-releasing hormone secretion by the hypothalamus, with changes in the dopaminergic and opioid systems found in patients with anorexia nervosa and in athletes [49].

Anovulation involves the production of unopposed estrogen without release of the oocyte or subsequent progesterone production from the corpus luteum. This state of unopposed estrogen can lead to endometrial hyperplasia with a possible increased risk of adenocarcinoma. In contrast to this hyperestrogenic state, athletic amenorrhea is usually associated with hypothalamic hypogonadism and a consequent hypoestrogenic effect. This hypoestrogenism, in turn, has been associated with osteopenia. In hypothalamic amenorrhea, FSH pulsations often predominate in contrast to the relative increase in LH versus FSH in anovulatory women with polycystic ovary syndrome. Patients with eating disorders tend to exercise excessively, leading to decreased sex hormone levels and subsequent bone loss [37]. Subnormal levels of insulin-like growth factor (IGF-1) and the adrenal steroid DHEA may be linked causally to the bone loss seen with anorexia nervosa [38].

Risk factors for amenorrhea

In a survey of 2156 students in eight high schools (94% Caucasian and aged mainly between 14 and 17 years), risk factors for secondary amenorrhea included binge–purging (odds ratio [OR], 4.17), weight loss and weight gain (OR, 2.59),

smoking at least one pack of cigarettes per day (OR, 1.96), being in the first year after menarche (OR, 1.74), weight gain of at least 4.5 kg (OR, 1.71), and weight loss of at least 4.5 kg (OR, 1.45) [50]. The younger the gynecologic age (years since menarche), the greater the likelihood of missing three consecutive cycles in the past year, with chronologic age less related to amenorrhea than gynecologic age.

Other factors involved in athletic amenorrhea

Athletic amenorrhea occurs more frequently in activities such as running, ballet, and gymnastics, in which intense physical training is combined with a desired lean body build [51]. The issue of athletic amenorrhea and delayed puberty in this group has raised the question of the ''chicken versus egg.'' Malina [52] challenged the hypothesis that these menstrual and pubertal abnormalities were caused by the intense exercise itself; instead, she raised the possibility that the lithe dancer's natural body habitus combined with environmental factors predisposed these teenagers to pubertal delay. One can further postulate that this cohort of girls is attracted by nature (build) and nurture (parental pressures) to such sports and is overrepresented in this population.

Intense training premenarchally has been associated with an increased risk of athletic amenorrhea. Frisch et al found that college athletes who began training before menarche had a higher incidence of delayed menarche and amenorrhea than athletes who began training postmenarchally [53]. The athletes who began training earlier also had limited caloric intake to a greater extent. Runners were found to experience more amenorrhea when compared with swimmers [53,54]. In a study of marathon runners, Shangold and Levine found that 24% of women had menstrual irregularity during training, with 19% having menstrual dysfunction before training. Of the runners with regular cycles before training, 93% continued to have regular cycles while training for the marathon [55]. In another study by Shangold and colleagues, luteal phase deficiency developed in one runner when she increased her mileage and returned to a normal cycle length when she decreased her mileage back to baseline [45].

In addition to intense physical exercise, several other factors contribute to athletic amenorrhea. Diet and nutrition can have a key role in maintaining regular menstrual cycles. In a study of preprofessional ballet dancers, total caloric intake was found to be as low as 1000 calories per day despite training 4 to 6 hours per day, 6 days per week [56]. Frisch et al found that amenorrheic competitive runners had an average intake of 1700 calories per day, whereas eumenorrheic runners consumed 2200 calories per day [53]. Decreased protein intake and lower meat consumption have been found in amenorrheic versus eumenorrheic runners [57]. Stress alone has been implicated in amenorrhea [58,59]. In a study of teenagers attending a private boarding school, 29.6% of students who had regular cycles at the start of the study experienced irregular periods in the year following their entry in boarding school [60]. Schwartz et al found that amenorrheic runners reported more subjective stress than eumenorrheic runners despite no detectable differences

on formal psychologic tests [61]. A study by Warren suggests that stress alone may not adequately explain menstrual dysfunction [51]. In a comparison of menstrual histories of preprofessional ballet dancers versus music students, presumably under equal competitive stress, Warren found that the ballet dancers had delayed menarche, whereas the musicians reached menarche without delay. Furthermore, dancers sidelined by injury began having menses despite no change in body weight, suggesting a possible "energy drain" caused by exercise [51,62].

Early data obtained by Frisch and colleagues suggested a "critical weight" or percent body fat necessary for menarche [63,64]. The theory postulated that 17% to 19% body fat was necessary to initiate menarche, with regular cycles maintained only when percent body fat remained above 22%. More recently, this theory has been disputed, with athletes maintaining menstrual flow with body fat as low as 4.7% [65]. Studies have focused on leptin, a hormone produced by fat cells that acts on hypothalamic receptors to control body weight, appetite, and energy expenditure. Leptin serves as part of a feedback loop in which the amount of energy stored is sensed by the hypothalamus, which then can adjust appetite and food drive to maintain weight. Leptin levels are high in obese children and adolescents, whereas reduced levels are associated with acute starvation and weight loss [66,67]. Leptin levels increase as puberty progresses and are higher in girls than in boys, just as body fat differences between the sexes differ with the progression of puberty. Leptin may act as the biologic link between nutritional status and reproductive function. Leptin levels are low in patients with anorexia nervosa when compared with controls and are highly correlated with body weight, body mass index, and percent body fat [67,68]. In patients with anorexia nervosa who are admitted to inpatient or partial hospitalization programs, leptin levels are initially low and increase with refeeding, partial weight gain [69], and resumption of menses [70]. Persistent amenorrhea in these patients is associated with low leptin levels despite weight gain.

Amenorrhea and osteopenia

Athletic amenorrhea results in a hypoestrogenic state associated with decreased bone density in adults and delayed or interrupted puberty with decreased bone density in teenagers [71,72]. The osteopenia, or significantly reduced bone mass, occurring with prolonged loss of menses has been associated with an increased risk of stress fractures in athletes and in patients with eating disorders [73,74]. In these groups of patients, the risk factors for osteopenia can be seen as a negative net balance between bone formation and bone resorption [73]. Increased bone loss through resorption occurs with hypoestrogenism (from amenorrhea) and hypercortisolemia (seen with chronic stress). Decreased bone formation occurs with glucocorticoid excess and with inadequate calcium and protein intake. Excess glucocorticoids may decrease calcium absorption from the gut and inhibit bone formation through direct receptor-mediated osteoblast effects [75,76]. The acquisition of bone mineral usually continues through the second decade, with peak bone

mass attained by late adolescence or early adulthood [77,78]. During the pubertal growth spurt, occurring at ages 11 to 14 years in most girls, approximately 40% to 60% of bone mass is acquired, with up to 5% more obtained during the third decade [79]. A mere 5% increase in bone mass has been associated with a significant decrease in fracture risk [79], and a 10% decrease in adult bone mineral density is associated with a two to three fold increase in fracture risk [73].

Osteoporosis is defined as a decrease in bone mass involving the osteoid matrix and the inorganic macrocrystalline component and leads to an increased risk of fractures, particularly of the vertebral bodies, proximal femur, and distal radius [39,80]. As many as 40% of postmenopausal women sustain at least one osteoporotic fracture, with over 1.3 million fractures occurring annually in the United States at a cost of $6 billion [39,81]. Although adult rates of eating disorders have not increased, the number of teenagers with recognized eating disorders continues to grow. The lack of attainment of adequate peak bone mass in these girls owing to an eating disorder in childhood or adolescence will result in increased costs of care for adults with osteoporosis. Although many of the medical changes associated with eating disorders are completely reversible with refeeding and weight gain and maintenance at an appropriate level, long-standing osteopenia may not be fully reversible.

Bone is constantly made and broken down by osteoblasts and osteoclasts, respectively. Cortical bone consists of tightly compacted plates of bone, whereas trabecular bone is more "spongy," with a honeycomblike network filled with varying fractions of red and yellow marrow [34]. Trabecular bone is more porous and is found at the end of long bones, in the spine, and in the femoral head. In anorexia nervosa, trabecular bone is more severely affected, with a relative sparing of cortical bone, most likely owing to the more rapid turnover of trabecular bone with resultant increased sensitivity to the metabolic changes caused by starvation or stress [73,77,82].

When explaining osteoporosis to young patients, it is often useful for the health care provider to discuss the person's skeletal status and the risk for osteoporosis not only in terms of bone loss but also in terms of the total amount of bone formation at skeletal maturity, or peak bone mass. Bone loss can be expected to occur at an annual rate of 1% from the fourth decade of life onward. To minimize the lifetime risk of fractures, a person should attempt to acquire the greatest amount of peak bone mass possible to maintain the mass above a critical threshold for fracture. The concept of the fracture threshold has been proposed by Wahner and colleagues, with the bone density fracture threshold set at 0.965 g/cm^2 for the lumbar spine; women with lower bone mineral density are at greatest risk [83]. Fractures should be infrequent when the bone mineral density exceeds the threshold; the further the value below the threshold, the greater the risk [84]. Although this concept of fracture threshold needs to be studied further, it can be a useful construct when explaining bone density issues to patients.

Peak bone mass is determined by inheritance and race, with African-Americans showing greater bone density than Caucasians. Gilsanz et al found increases in bone density in Caucasian and African-American girls during puberty, with the

latter group showing a greater magnitude of increase in weight and vertebral bone density by the end of puberty [85]. Peak bone mass is also determined by muscle strength, physical activity, circulating estrogens and androgens, dietary calcium, and weight and height. Data obtained by Bonjour and colleagues and Theintz et al confirm that a marked acceleration in bone mass accumulation occurs in early adolescence during the pubertal growth spurt [86,87]. Theintz believed that little bone mass was accumulated after 15 years of age at Tanner stage 5 (sexual maturity rating 5, or adult). In contrast, in a 5-year study of 156 college-aged women attending professional schools, Recker et al found that 6.8% of lumbar bone mineral density and 12.5% of total body bone mass were acquired in the third decade of life. The estimated age in their study for the cessation of bone mineral acquisition ranged from 28.3 to 29.5 years [79]. The cessation and the continuation of mineralization are thought to be possible, depending on modifiable habits such as physical activity, smoking, and dietary factors [79,88,89]. Slemenda and colleagues noted that pubertal gains in skeletal mineralization were particularly site dependent, with marked gains more common in areas of predominantly trabecular bone (eg, the lumbar spine). Increases in weight correlated with increases in trabecular bone, whereas height was found to correlate more strongly with cortical bone changes [88].

Lloyd et al [90] found that calcium supplementation correlated with increased gains in adolescent bone mass. Rubin et al [91] confirmed a positive impact on bone mass acquisition in girls with calcium intake and physical activity. Recker et al found that the rate of bone density gain correlated positively with calcium and protein intake and physical activity and negatively with age [79]. Oral contraceptive use was associated with a greater gain in total body bone mass.

Osteopenia, amenorrhea, and exercise

Osteopenia has been associated with amenorrhea of relatively brief duration. Bachrach et al found that 12 of 18 girls with anorexia nervosa were osteopenic, with half of this group diagnosed in the previous year [77]. Their findings suggested that osteopenia developed relatively quickly, or that each patient had unrecognized illness for a longer period of time. The duration of illness and the age at onset of anorexia nervosa correlated significantly with bone density, whereas the activity level, duration of amenorrhea, and calcium intake did not show a significant relationship with bone density. In contrast, Rigotti et al found that exercise protected against bone loss in anorexia nervosa [35]. Weight-bearing exercise is thought to be more protective than non–weight-bearing exercise [92]; however, when exercise leads to amenorrhea, the benefits are lost [39]. Cann et al discovered osteopenia in young adult women with exercise-related amenorrhea by performing CT of the spine [93]. A longer duration of amenorrhea correlated with lower spinal bone mineral density. Neither high calcium intake nor physical activity seems to compensate for the lack of bone mass accretion occurring in late-maturing amenorrheic athletes [38].

Drinkwater et al used dual-photon absorptiometry to establish that amenorrheic runners had lower spinal bone mineral density when compared with eumenorrheic runners, despite no differences in calcium intake, years of training, frequency and duration of training, percent body fat, or menarchal age [94]. The amenorrheic individuals were running 67.3 km per week as compared with 40.1 km per week by the eumenorrheic runners. No correlation was found between estradiol levels and bone mineral density. These same patients were then re-evaluated in a follow-up study 2 years later [95]. Nine of the 14 amenorrheic runners were re-evaluated, with 7 of these women having spontaneously resumed menses. These now-menstruating runners had decreased their training mileage by 10% and increased their body weight by 1.9 kg, with each runner showing a significant increase in bone density of 0.071 g/cm^2 ($P < 0.01$). The two runners with persistent amenorrhea displayed a further decrease in bone density. The eumenorrheic runners still had significantly higher bone densities than the initially amenorrheic runners who had resumed menses (1.369 versus 1.198 g/cm^2) despite gains of 6.2% in bone mineral density over a period of 14.4 months.

Wolman et al found greater gains in bone mineral density in eumenorrheic girls than in amenorrheic girls. Although calcium intake did not differ between the groups, increased intake was associated with increased bone mineral density [96].

Hypoestrogenism in postmenopausal women has been shown to have dual effects [34]. First, intestinal and renal calcium homeostasis becomes less efficient and results in an increased calcium intake necessary to maintain calcium balance. Second, bone cells have been shown to contain estrogen receptors [97], and a deficiency in estrogen may allow osteoclasts to resorb bone with greater efficiency, leading to a net bone loss.

Biller et al found a correlation between increased urinary cortisol excretion and decreased spinal bone mineral density, suggesting that hypercortisolemia may have a role in trabecular bone loss [34]. Glucocorticoid excess, seen in runners and other athletes and in teenagers with anorexia nervosa, causes increased bone resorption and may inhibit bone formation [49].

Estrogen, menses, and bone density

Drinkwater et al found a possible dose–response to menses, with increasing numbers of cycles per year associated with a linear increase in bone mass [98]. Vertebral bone mineral density was significantly lower in athletes with lifetime histories of irregular menses when compared with eumenorrheic athletes. The lowest bone mineral densities occurred in athletes with lower serum estradiol levels, lower progesterone levels, lower body weight, later menarche, earlier initiation of training, younger age, and a greater number of miles of training per week. These data support current research findings suggesting that peak gains in bone density occur in early puberty (ages 11 to 14 years). An arrest of bone deposition or an increase in bone resorption at this stage would result in a greater

loss than in later years when less bone is expected to be deposited. Female athletes with oligomenorrhea had a bone density 6% less than eumenorrheic girls (1.18 g/cm^2 versus 1.27 g/cm^2); runners who had always been irregular had bone mineral densities that were 17% lower (1.05 g/cm^2). The combination of body weight and menstrual pattern predicted 43% of the total variation in lumbar density. These data suggest that even a one- to two-cycle increase in annual menses may improve a female athlete's skeletal health.

Protective effects of exercise: possible site-specific effect

Conflicting data exist regarding the issue of site-specific sparing of bone density caused by exercise. Slemenda and Johnston studied high-level skaters aged 10 to 23 years and compared them with 22 sedentary girls [99]. Increased bone mineral densities were found in the trunk, legs, and pelvis of the skaters, whereas the spine, ribs, and arm bone mineral densities were not significantly different. There were no statistically significant differences in height or weight, but body fat was significantly less in the skaters (18.7% versus 24.3%, $P = 0.0004$). Oligomenorrhea was reported in 40% of the skaters, with all of the sedentary girls cycling regularly.

In a study of amenorrheic versus eumenorrheic rowers, Wolman et al found that rowing partially compensated for the adverse effects of amenorrhea [100]; however, mean trabecular bone mineral density remained lower in amenorrheic versus eumenorrheic athletes. Young et al found that cortical weight-bearing areas such as the proximal femur were less affected by hypogonadism in weight-bearing athletes; however, trabecular areas of weight bearing, such as the lumbar spine, were not protected [101]. No benefit was found in non–weight-bearing areas of cortical bone (eg, ribs, arms, and skull).

Myburgh et al used DEXA to compare 25 athletes (19 female, 6 male) with confirmed stress fractures matched for age, sex, weight, height, and exercise history with 25 control athletes who lacked a history of fracture [102]. Bone mineral density was significantly lower in the athletes with a history of stress fracture (spinal bone mineral density, 1.01 g/cm^2 versus 1.11 g/cm^2; femoral neck bone mineral density, 0.84 g/cm^2 versus 0.90 g/cm^2). Spine bone mineral density was less than 90% of the predicted age-related value in 8 of 25 athletes with fractures. No athlete in the control group had less than a 90% predicted age-related value. Three of the athletes in the fracture group had bone mineral densities that were at least two standard deviations below the predicted level. Although the age of menarche was similar, half as many women had used oral contraceptives in the fracture group when compared with the control group, with seven of the women in the fracture group versus no woman in the control group having irregular periods. Calcium intake also differed significantly between the groups. The fracture group ingested 697 mg daily, whereas the control group took 832 mg. Mybergh et al had previously found that shin soreness in the male and female athletes was associated with low dietary calcium intake [103].

Reversibility of bone loss in anorexia nervosa

It is not known to what extent osteopenia is reversible in girls and women with the female athlete triad. In a cross-sectional study of predominantly adult women with anorexia nervosa, Treasure et al found that bone mineral density improved with increasing weight and was normal in weight-recovered individuals [104]. In a prospective longitudinal study of 27 women with anorexia nervosa, Rigotti and colleagues found no significant increase in cortical bone density after a median follow-up of 25 months [105]. Although most of the patients had gained weight, only 11 of 27 had reached 80% or more of ideal body weight, with six patients resuming menses. The study by Rigotti et al is limited by the lack of data on trabecular bone, the site more sensitive to bone resorption and formation. Bachrach et al [77] studied 15 teenagers with anorexia nervosa prospectively for 12 to 16 months. Although bone mass increased with weight gain, osteopenia persisted in 8 of 15 patients, with only 2 of these girls resuming spontaneous menses. In a separate study, Bachrach et al found normal values in the lumbar spine and in whole body bone mineral density in nine clinically recovered women with anorexia nervosa, although three of the nine women still had osteopenia of the spine [106]. The data obtained by Drinkwater et al also suggest that lowered bone mineral density is at least partially reversible, although it is not clear whether a person can regain the amount of bone expected to be accrued in early adolescence [95,98]. Jonnavithula et al studied nine amenorrheic and 21 normal women, aged 13 to 29 years, including 17 dancers and 13 sedentary subjects [107]. Amenorrheic dancers displayed the greatest increase in spinal bone mineral density, with a gain of 9.65% in the first year and further gains of 4.49% in the second year. None of these women received exogenous estrogen. Despite these gains, amenorrheic dancers continued to have significantly lower bone mineral density values than eumenorrheic or sedentary women. Bone mineral density gains were most significant in the two subjects who gained weight and resumed irregular cycles (three in a 12-month period). It was concluded that young amenorrheic exercising women could increase bone mass even before resuming menses.

Klibanski et al studied the use of estrogen replacement therapy in anorexia nervosa. Patients aged 16 to 43 years with amenorrhea of at least 6 months' duration were randomized to no therapy versus estrogen and progestin [108]. The latter group received mainly conjugated estrogen in the form of Premarin, 0.625 mg daily. DEXA was performed at L1-L4 using the same scanner at 6-month intervals. Age, the duration of amenorrhea (3.3 versus 4.6 years), percent body fat (15% versus 14%), percent ideal body weight (72% for both groups), and the duration of follow-up (1.6 versus 1.4 years) were not statistically significant between the groups. Although there was no significant difference in bone density in the estrogen-treated and non–estrogen-treated groups, a difference was observed when women who had recovered weight were excluded from analysis. In the patients with an initial body weight of less than 70%, a 4.0% increase in mean bone mineral density occurred with estrogen treatment. In contrast, control patients with a comparably low initial body weight who did not receive estrogen had a 20.2%

decrease in bone mineral density. Women in the control group with spontaneous resumption of menses had a 19.3% increase in bone mass, with each woman in this group having an initial percent ideal body weight above 70%. Klibanski and colleagues concluded that estrogen replacement therapy would not prevent progressive osteopenia in this group, whereas a subset of patients with exceedingly low body weight may benefit from exogenous estrogen and progestin therapy.

Kreipe and colleagues found little benefit from estrogen therapy without accompanying weight gain in a study of bone biopsy specimens obtained from four young women with anorexia nervosa, two receiving hormone replacement therapy and two without this therapy [109]. These data may have been confounded by body weight; the two women on hormone replacement therapy were at 78.5% normal body weight versus 86.5% normal body weight in the other two patients [109,110]. Moreover, the use of hormone replacement therapy and subsequent withdrawal bleeds may give the adolescent and her mother a false sense of security, decreasing further motivation to gain weight [111]. The method of delivery becomes relevant here. The use of a transdermal estrogen patch or continuous hormone pills with withdrawal bleeds only quarterly may minimize the stress of periods in these patients. Harel and Riggs [112] observed a girl with anorexia nervosa who showed no improvement in bone density despite oral contraceptive therapy (with good compliance according to the two researchers). After switching to transdermal estrogen, the lumbar bone mineral density increased [112]. In this study, an Estraderm patch was used in a dose of 0.05 mg for 2 months, followed by 0.1 mg applied to the abdominal wall weekly for 3 weeks, with oral medroxyprogesterone acetate, 10 mg per day, given on days 12 to 21 of the cycle. The transdermal patch has the advantage of no first pass through the liver, reducing the subsequent increase in sex hormone–binding globulin or IGF-1 [110].

Future fertility in patients with eating disorders

Fertility should return to normal in girls and women who achieve normal weights in recovery from an eating disorder [113,114]. Stewart and colleagues found that 16.7% of 66 patients in their infertility clinic had disordered eating; many of these patients expressed fears that their eating disorder had "damaged their bodies" [115]. In older women, concerns over future fertility may be a useful stimulus for behavior change and weight improvement. In the concrete-thinking adolescent who is unable to foresee consequences, future fertility may be too abstract to contemplate. Patients who have a history of eating disorders should be monitored closely for a recurrence of symptoms during pregnancy and postpartum.

Treatment of the patient with an eating disorder

For underweight athletes with amenorrhea and eating disorders, the best course of action is to improve their eating habits and nutritional status. Menses will often

resume at the weight at which they ceased, providing a relative weight goal for many of these women. As suggested by data obtained by Warren, a gain in percent body fat may not be necessary for the resumption of menses [51]; however, increases in dietary intake to provide sufficient caloric intake to meet energy expenditure seem reasonable, even in women of normal weight. Calcium intake should be at least 1200 mg/day (three to four glasses of milk or calcium-supplemented orange juice, or as a chewable supplement such as Tums), although some researchers suggest that this value should be increased to 1500 mg/day [30,116,117]. Adequate iron and protein consumption must also be encouraged, because many athletes with the female athlete triad avoid red meat and other forms of animal protein in an effort to ''eat healthy.''

Although many of these athletes should decrease their level of training to a point at which menses would resume, many girls are unwilling to sacrifice their training schedule and, in fact, do not welcome menstrual periods. In this group, cyclic estrogen and progestin replacement should be considered for women who are hypoestrogenic, although data on the benefits of estrogen in the absence of weight gain remain controversial. The optimal regimen for estrogen replacement therapy remains debatable. Conjugated equine estrogen (Premarin) at a dose of 0.625 to 1.25 mg/day for days 1 to 25 per month can be combined with medroxyprogesterone at a dose of 10 mg per day from days 14 to 25. The transdermal estrogen patch is more widely used, with the main side effect being local irritation or chafing during activity. Many adolescents prefer this method, because they are less likely to be bothered with periods. For adolescents who are also sexually active, low-dose combination oral contraceptives can be used or the contraceptive patch (Ortho Evra, Ortho-McNeil Pharmaceutical, Inc., New Jersey). In the amenorrheic woman who currently makes estrogen but does not ovulate, cyclic use of Provera for 12 to 14 days every few months can prevent endometrial hyperplasia.

In the teenager with delayed puberty and primary amenorrhea, the schedules for estrogen replacement described previously may not be optimal for growth and pubertal development. Advancing estrogen levels too quickly may precipitate premature closure of the epiphyses in younger girls. Many of these girls go through adrenarche at the normal time. In girls who are not making estrogen, a gradual increase in estrogen mimicking puberty may give better cosmetic results for breasts. Conjugated estrogen (Premarin), 0.3 mg, could be given daily for several months, followed by Premarin, 0.625 mg daily (days 1–25), with medroxyprogesterone added 5 days a month (days 20–25), with a subsequent increase in progestin to 10 to 14 days per month (days 15–25) [118]. For girls who want to augment breast development, after 3 to 6 months, the conjugated estrogen can be increased to 0.9 mg/day, and then eventually to 1.25 mg/day. Unfortunately, many girls with the athletic triad prefer their prepubertal figure and have no motivation to change their shape. Moreover, many of these girls fear weight gain and associate the use of estrogen or combination oral contraceptive pills with direct weight gain. A focus on stress fracture prevention and healthy bones can help promote weight gain in an attempt to preserve or improve athletic performance.

Eating disorders can cross generational lines, with nature and nurture combining to perpetuate a cycle. When an eating disorder is suspected in the parent of an adolescent, family therapy can help the parent to acknowledge her needs as different from those of her child, including different energy and exercise needs.

If greater than 30% of ideal body weight has been lost, or if the patient experiences new bradycardia with or without orthostatic hypotension, hospitalization should be considered. Criteria for hospitalization are as follows:

Sinus bradycardia, rate less than 50 beats per minute
Other arrhythmia, including prolonged corrected QT interval
Hypothermia (temperature $<97.5^{\circ}$F)
Orthostatic hypotension by pulse or by blood pressure
Precipitous weight loss in a short time period
Dehydration
Failing outpatient management
Severe electrolyte imbalances (potassium <3.0, phosphorus <2.0)
Unable to eat or drink, acute food refusal
Suicidal ideation or acute psychosis
Intractable vomiting
Comorbid diagnosis interfering with treatment of the eating disorder (eg, major depression, obsessive–compulsive disorder, severe family dysfunction)

The main goals of treatment include medical stabilization, weight restoration, and weight maintenance, depending on how underweight the person is at the start of therapy. A multidisciplinary team approach works most efficiently to promote recovery. Better prognosis is associated with younger age, less weight loss, and shorter duration of illness; a worse prognosis is associated with vomiting, a history of extreme or precipitous weight loss, and depression. A full review of the specific treatment of eating disorders is beyond the scope of this article and can be found elsewhere [28–30,119–121].

A growing body of literature exists on the use of the bisphosphonates in postmenopausal osteoporosis [122]. These agents alter the rate of bone turnover, affecting the number and activity of osteoclasts or their precursors and functionally inhibiting osteoclastic activity [123]. At a biochemical level, recent research suggests that these drugs alter intracellular biochemical messengers and impair in vitro bone formation [124,125]. Some studies also show that bisphosphonates impair macrophage production of interleukin-1, a potentially powerful regulator of skeletal function, although not all studies support this conclusion [122,126,127]. Intermittent cyclical use of etidronate was shown to increase spinal bone mass and reduce the incidence of new vertebral fractures in a prospective, double-blind, placebo-controlled study of women with postmenopausal osteoporosis [128]. Storm et al found significant increases in bone density and decreases in fractures associated with the use of etidronate versus placebo in postmenopausal women with osteoporosis [129]. These results were confirmed in a third study by Harris et al [130].

Alendronate (4-amino-1-hydroxybutylidine-1,1-bisphosphonate) is a highly potent inhibitor of bone resorption, functioning at 100 to 500 times the strength of etidronate [131,132]. Moreover, alendronate acts as a highly selective inhibitor of resorption, with no associated defects in bone mineralization, producing increases in the mass and strength of bones in animal models of postmenopausal osteoporosis [132–134]. Although etidronate therapy has been associated with an initial increase in bone mineral density followed by a plateau in postmenopausal women [128], alendronate in doses of 5 to 10 mg daily has been associated with a progressive increase in bone mineral density at the spine and hip in postmenopausal women with osteoporosis, with ongoing increases through the second year of treatment [131]. Studies are underway to address the role of the bisphosphonates in premenopausal women with anorexia nervosa and osteopenia. These drugs may be difficult to use in women with the athletic triad, because they must be taken on an empty stomach and may provoke gastrointestinal complaints, including bloating, dyspepsia, and diarrhea.

The next step

Several questions remain with respect to the female athlete triad. The first question is who should be studied with dual-photon absorptiometry, and, if other improved technologies become available, at what cost should they be performed. Currently, patients with amenorrhea of 6 to 12 months' duration should be studied with DEXA if there is little ongoing improvement in weight gain. In women with amenorrhea lasting longer than 12 months, the DEXA can be used to provide a baseline and to serve as a reality check for the patient in strong denial of a problem.

A second question is who should be started on estrogen replacement therapy, in what form, and for how long. In the absence of weight gain, estrogen therapy may be of limited to no benefit. Suggested regimens have been noted herein, but few data exist to compare the different regimens. Unanswered questions remain about the use of DHEA and the bisphosphonates.

A third question involves the use of calcium and the recommended standard dose of 1200 mg versus the 1500 mg dose suggested by Key and Matkovic [116,117]. As noted in several studies, many girls and women consume considerably less than that amount, although even differences below the level of 1200 mg seem to provide a benefit. The current best dietary practice suggests the use of supplements spread throughout the day, with no one dose greater than 500 mg. The optimal timing and dosing in this population have not been adequately addressed to date.

A final question is how one can best motivate adolescents and young adults with the female athlete triad to change the following modifiable factors: smoking, dietary factors (adequate calcium, protein, iron), weight gain or loss, exercise intensity, possible supplemental estrogen.

With early recognition and management, the cost of care for patients (physically and fiscally) and for society may decrease. Given the growing number of

individuals aging and with a history of the female athlete triad, new solutions to the questions of bone density and speedy recovery from an eating disorder become imperative. Strategies for the primary prevention of eating disorders and osteopenia, for the secondary prevention of sequelae, and for tertiary interventions once disease manifests can improve the health of generations of women to come.

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Adolescent endometriosis

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The history of adolescent endometriosis in the medical literature is very brief. Bullock et al [1] identified endometriosis in adolescent patients in 1973 by culdoscopy and laparoscopy. Later, Goldstein et al [2] and Chatman and Ward [3] described endometriosis in adolescents in the late 1970s and early 1980s. Since the 1980s the diagnostic work of adolescents with chronic pelvic pain, severe dysmenorrhea, and irregular bleeding has been very aggressive and has included laparoscopic examination and destruction of endometriosis. During the late 1990s it was realized that most adolescent endometriosis is minimal or mild and does not respond well to surgical maneuvers. Therefore, aggressive medical management of pain and dysmenorrhea is incumbent before laparoscopic intervention in most patients. Also, several of these patients have to be treated medically for control of their symptoms even after laparoscopic removal of the implants as conservation of the reproductive organs and control of the progression of endometriosis are the hallmarks of treatment in adolescents. For a quarter of a century adolescent endometriosis has been recognized as a cause of pelvic pain; its diagnosis and treatment continues to evolve.

Incidence

Multiple investigators reported the incidence of endometriosis in adolescents [2–5]. The mean age of adolescents in these studies is between 11 and 22 years of age. They presented with chronic pelvic pain or dysmenorrhea and were treated unsuccessfully with nonsteroidal anti-inflammatory drugs or oral contraceptives pills (OCP). Subsequently a laparoscopic examination was performed to evaluate the cause of pelvic pain. In a retrospective study by Goldstein et al [2] on 146 white adolescents, endometriosis was seen in 47% of the patients. In 1982,

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Chatman and Ward [3] reported a 65% incidence of endometriosis in Chicago in a group of 43 black teenagers. In 1980, we reported a 20% incidence of endometriosis in 96 white teenagers in whom a laparoscopy had been performed for chronic pelvic pain [4]. Data from Boston Children's Hospital between 1974 and 1983 showed the incidence of endometriosis to be 45% [5].

In more recent studies, investigators are more attuned to the existence of atypical endometriosis, especially in younger patients. In 1989, Vercellini et al [6] described a 38% incidence rate of endometriosis among 47 adolescent patients. This study was conducted between 1983 and 1987; the classification was changed to include atypical lesions about half way through the study. Their revised estimate of the incidence of endometriosis was changed to 52% from 38.8%. Similarly Laufer et al [7] reported an incidence of 67.4% for patients seen at Children's Hospital in Boston between 1990 and 1994. Emory's experience reported by Reese et al [8] in 1996 quoted an incidence of 73% in 67 adolescents. Thus a significant proportion of adolescents with chronic pelvic pain that is unresponsive to medical therapy are found to have endometrial implants.

Diagnosis

The average age at presentation for endometriosis is 15.9 years. Rare cases of endometriosis in premenarchal patients have been described. This would negate retrograde menstruation as the sole cause of endometriosis. In Reese et al's [8] study, 95% of their patients had cyclic and acyclical pelvic pain, 94% had dysmenorrhea, 25% had irregular menses, 29% had deep dyspareunia, 43% had abdominal pain and nausea, and 3% had constipation and diarrhea [8]. Other investigators, such as Goldstein et al [2] and Chatman and Ward [3], reported the same experience. The pain is usually disruptive and interferes with school, sports, and other social activities. These patients may have had at least three episodes of lower abdominal pain for which they were seen in the emergency room or the doctor's office. Usually, scant physical findings are obtained at these visits. The lab findings are also within normal limits. Dysmenorrhea can last for 3 to 4 days. Abnormal bleeding is usually accompanied by cramping, probably related to increased prostaglandin formation by the endometrial implant. Dyspareunia usually is described as deep and the bowel symptoms may be clustered around the time of abnormal bleeding.

Laufer et al [7], in a retrospective chart review of 46 patients, were unable to show any difference in the presenting symptoms of adolescent patients with and without endometriosis. The only statistically significant finding was that six patients without endometriosis complained of irregular menses compared with three patients with endometriosis. This study had very small numbers and was retrospective but it clearly emphasized the fact that further prospective studies need to be done to illuminate any symptoms that are typical of adolescents with endometriosis.

A history of endometriosis in the family should prompt further questioning and raise the index of suspicion. The heritable aspects of endometriosis were first

demonstrated by Malinak et al in 1980 [9]. They concluded that any asymptomatic girl with a first-degree relative (mother or sister) with endometriosis should be counseled that her own risk of developing endometriosis is 7% greater than normal, which is approximately 1%. If the relatives had endometriosis that was very severe, then the girl's risk for severe endometriosis was significantly higher than if none of her first degree relatives had endometriosis. This fact is common knowledge with the patients and creates quite a concern for mothers and families of such adolescent patients.

Physical examination of an adolescent with endometriosis can vary from a normal examination to generalized pelvic tenderness or occasional, adnexal masses. Goldstein et al [2] reported a normal pelvic examination in 17% of the patients, whereas Chatman and Ward [3] described no abnormal physical signs in 7% of the patients. Goldstein et al [2] noted pelvic tenderness in 76% of their patients; Reese et al [8] described 95% of their patients as having diffuse tenderness. They also found localized tenderness in 77.6%, cul-de-sac nodularity in 1.5%, and adnexal thickening in 15%. The adnexal masses that were found in these series of patients are primarily benign cysts and endometriomas. Chatman and Ward [3] detected adnexal masses in 11% of their adolescent patients whereas Reese et al [8] palpated adnexal masses in 22% of their patients with chronic pelvic pain. In this series, benign ovarian cysts were noted in 17.9% (12 out of 67) and large endometriomas were noted in 13.4% (9 out of 67 patients) of patients.

The aforementioned studies indicated that neither the pelvic examination nor physical symptoms can provide reliable information about the existence of nonovarian endometriosis. A thorough history and physical examination must be done primarily to rule out other causes of pelvic abdominal pain. Because endometrial implants were detected in nonsymptomatic women who were undergoing tubal ligation, the existence of implants does not necessarily implicate them as the source of pelvic pain. Thus, other causes of pelvic pain must be investigated.

A pelvic ultrasound is indicated in the evaluation of pelvic pain, but it is not helpful in the diagnosis of nonovarian endometriosis [10]. A pelvic ultrasound may reveal an obstructive anomaly or adnexal mass, which may have been difficult to detect on physical examination. Although CA-125 is elevated in patients with endometriosis, other pelvic pathologies can cause a similar increase in this cell surface antigen. Thus, it is too insensitive for diagnosing endometriosis. Some investigators have advocated using CA-125 to detect recurrence of endometriosis. The long-term nature of this disease in the adolescent may make CA-125 a valuable tool in the evaluation of the adolescent with recurring pain; however, further research is necessary.

The current focus of research is on nonsurgical means of detecting endometriosis. Most parents are very concerned about subjecting their children to laparoscopy for diagnosis. Investigators are actively searching for peritoneal fluid or serum markers, that may accurately and noninvasively detect endometriosis [11]. Unfortunately such markers are currently not available. Ling [12] was able to successfully identify 78% of women with endometriosis on the basis of a

careful history and physical examination, at least 6 months' duration of noncyclical pain, nonresponsive to OCP and NSAIDS, normal laboratory and ultrasound studies. A diagnostic and treatment algorithm was proposed where patients with clinically suspected endometriosis may bypass the initial diagnostic laparoscopy and instead are placed on 3 months' of gonadotropin-releasing hormone agonist (GnRH-a). Laparoscopy is recommended only if there is no diminishment of pain. Certainly other causes of pelvic pain, such as irritable bowel syndrome, may respond to GnRH-a therapy. Thus, the decreased cost and risk of GnRH-a therapy is counteracted by the loss of definitive diagnosis, which comes with laparoscopy.

Surgical diagnosis

In most instances, surgical evaluation of the pelvis is necessary when the adolescent has failed to respond to oral contraceptive pills and nonsteroidal anti-inflammatory drugs.

Findings

Laparoscopic evaluation of the pelvis commonly reveals atypical, endometriotic lesions. Redwine [13] demonstrated a wide array of endometriotic appearance, and a change in endometriotic appearance with increasing female age. Atypical, endometritic lesions include clear papules, red, flame-like lesions, white lesions, and glandular lesions. Clear papules and red lesions are more likely to be found in younger patients. Because clear, papular lesions may be difficult to visualize, Laufer [14] described the technique of filling the pelvis with fluid and visually inspecting the pelvis laparoscopically "under water" [14]. In one study, 55% of patients had subtle endometriosis [15]. Subtle endometriotic lesions were the only lesions seen in 40% of Redwine's [13] patients. Thus the laparoscopist must be vigilant in the scrutiny of the pelvis.

In a recent article, Walter et al [16] demonstrated a positive predictive value of only 45% for the detection of endometriosis visually. The American Society for Reproductive Medicine (ASRM) edometriosis scores decreased significantly when histologic, rather visual scores, were used to stage endometriosis. They recommended biopsying all abnormal areas to ensure the correct diagnosis of endometriosis. Because only 2 out of 380 normal-appearing peritoneal biopsies had microscopic endometriosis, routine biopsy of normal-appearing peritoneum may not be indicated in patients with chronic pelvic pain. In contrast, Murphy et al [17] demonstrated that 25% of specimens that appeared normal were found to contain endometriosis by way of scanning electron microscopy. In our practice we biopsy nontypical lesions but not normal peritoneum.

Staging

Staging allows for quantification of the amount of endometriosis present at the time of laparoscopy. The revised ASRM classification of endometriosis is used to stage endometriosis by way of a point system [18]. Multiple studies confirm the

existence of primarily low-stage disease in adolescent patients. Stage I disease may be found in 79.6% of adolescents with endometriosis. Stage II disease is noted in 12.3% of patients [8]. The extent of endometriotic implants is not a reliable indicator of the degree of pain or the prognosis with treatment [19]. The severity of dysmenorrhea does not relate to the number of endometrial implants. Vernon et al [20] showed that red lesions are more metabolically active than the black or brown ones. These lesions produce more biochemical substances, such as prostaglandins. Increased prostaglandin F was directly linked to intense, smooth muscle contractions, including bowel and myometrial contractions.

Only 6.1% and 2.0% of Reese et al's [8] subjects had stage III and stage IV disease, respectively. None of these patients was younger than 16 at the time of diagnosis, and none of them had an obstructive mullerian anomaly. Subjects with obstructive mullerian anomalies are more likely to present with stage III or IV disease; however, with relief of the obstruction the lesions regress spontaneously [21]. In light of this fact we maintain a nonaggressive attitude when dealing with endometriosis in patients with obstructive mullerian anomalies. We do not ablate or excise endometrial implants at the time of pelvic reconstruction. In the majority of cases, with relief of obstruction, these patients become asymptomatic and pain free.

Management

Pain management is the primary goal of treatment in the adolescent. The secondary goal is maintenance of fertility. Most patients express concern that the lack of diagnosis and treatment might lead to more extensive disease and subsequent infertility. Medical and surgical options are available for the management of endometriosis. In our practice we advocate prolonged medical therapy following surgical diagnosis and excision of endometriosis. There are currently no published randomized studies that compared the efficacy of medical versus surgical treatment of pain secondary to endometriosis. There is a paucity of scientific evidence that pertains to the treatment of endometriosis in the adolescent. The following quoted investigations were performed primarily on adults. Medical treatment induces atrophy of the hormonally-dependent, ectopic endometrium, whereas surgical therapy strives to permanently destroy or remove the tissue. Unfortunately, the duration of hormonal therapy is limited by its side effects and repetitive surgery can ultimately be detrimental to the patient's fertility status. Because the presence of implants does not necessarily correlate with pelvic pain, it is difficult to compare various treatment protocols.

Medical

Oral contraceptive pills

Because of its low side effect profile and its ability to be taken indefinitely, OCPs are typically the first line of therapy in adolescents. There is little scientific

evidence to support the use of OCPs for endometriosis, however. Taken cyclically, OCPs decrease the endometrial lining and thus decrease the amount of tissue that produces prostaglandins, and also suppress ovulation and the subsequent, luteal phase symptoms, of endometriosis. Taken continuously, OCPs can decidualize endometrial implants and cause regression of symptoms [5]. When severe dysmenorrhea is the primary complaint, continuous OCPs may induce amenorrhea and subsequent relief of symptoms [22]. This therapy is only suppressive and not curative.

In a study that compared the use of cyclic OCP to gonadotropin releasing hormone agonist (GnRH-a), Vercellini et al [23] demonstrated a similar decrease in nonmenstrual-associated pain and dyspareunia in both groups. Symptom recurrence was common after stopping therapy for 6 months. Irregular bleeding is the most common side effect. This is the mainstay of our treatment after surgical diagnosis and excision.

Progestational agents

Progestational agents include medroxyprogesterone acetate (MPA) and 19-nortestosterone derivatives, such as norethindrone and norgestrel. These agents cause decidualization of ectopic, endometrial tissue and subsequent atrophy. In humans, 100 mg of medroxyprogesterone acetate daily caused complete resolution of endometriotic lesions in 50% of patients, whereas only 12% resolution was noted in the group that took placebo [24]. A pain relief rate of 90% was noted with progestational therapy [25]. Medroxyprogesterone acetate may be given in oral forms of 20 to 30 mg daily or the depot form of 150 mg every 3 months. Vercellini and his colleagues [26] compared depot MPA 150 mg with low-dose, oral contraceptive pills plus low-dose danzol 50 mg. Both groups of patients had significant decreases in pain after 6 months of treatment; however, between 15% and 65% of subjects reported side effects from the depot MPA. Unfortunately, no long-term studies have evaluated the outcome of patients after stopping depot MPA treatment. The existing studies followed patients for a maximum duration of 6 months to a year.

The relatively low side effect profile of progestational agents makes them a good choice in the long-term management of endometriosis in adolescents. The most common side effect is abnormal vaginal bleeding which may be controlled with short bursts of estrogen therapy. Although resulting weight gain and acne are certainly areas of concern for the adolescent, few patients have discontinued the use of depot MPA in the face of significant decrease in their pain. Other side effects include breast tenderness, water retention, and depression. There is concern over the impact of long-term use of MPA on high-density lipoprotein and bone density [27]. We are currently aware of at least one study that is underway to investigate the long-term impact of depot MPA use on bone density in adolescents.

Endometriosis was treated successfully with other progestational compounds, such as dydrogesterone, norethindrone acetate, and cyproterone acetate. All agents decreased pain scores significantly and have a similar side effect profile. Because compliance with medication may be more problematic in the adoles-

cent population we typically use depot MPA (Depo Provera) instead of any of the oral formulations.

Danazol

Danazol decreases the volume of ectopic, endometrial tissue by inducing a hyperandrogenic state. The Cochrane Database of Systematic Reviews identified four randomized, controlled trials in which danazol was compared with placebo or no therapy; the main outcome was pain improvement. Its concluding results were that danazol diminished pain symptoms, but the irreversible,androgenic side effects were substantial [28]. These side effects would be intolerable for an adolescent who is considering long-term therapy, therefore, we typically do not offer this therapy to this population.

Gonadotropin-releasing hormone agonists (GnRH-a)

Gonadotropin-releasing hormone agonists create a hypoestrogenic, hypogonadal environment, which is not conducive to growth of ectopic endometrium. A recent Cochrane database of systematic reviews determined the effectiveness of GnRH-a in the treatment of pelvic pain secondary to endometriosis [29]. Studies that compared the use of GnRH-a versus placebo or no treatment showed use of GnRH-a caused decreased pain scores [30]. A 6-month duration of treatment is typically recommended. Hornstein et al [31] compared pain recurrence in women who were treated with natarelin for 3 months versus 6 months. They could not demonstrate an association between duration of GnRH-a therapy and rate of pain recurrence. Waller and Shaw [32] reported the longest follow-up period. After 6 months of therapy with GnRH-a, patients were followed for up to 7 years. The likelihood of recurrence of symptoms was 10% after 1 year and 50% after 5 years. GnRH-a and danazol seem equally effective in controlling endometriosis symptoms; however, their side effects differed significantly.

Common side effects of GnRH-a are related to the creation of the hypoestrogenic environment. These include hot flashes, insomnia, and vaginal dryness. Unfortunately, GnRH-a cannot be used indefinitely because of the concerns about its effect on bone density. A decrease in bone mineral density of 3% after 6 months of GnRH-a therapy was reported in the adult population [33].Because adolescents have not yet reached their maximal bone density, a more serious impact on bone density may be expected in the adolescent who uses long-term, GnRH-a therapy. In addition, long-term, medical management of endometriosis may necessitate repeated courses of GnRH-a therapy. These patients should be encouraged to use strategies, such as performing weight-bearing exercise, increasing calcium and vitamin D intake, and ceasing smoking and alcohol consumption, that may help to diminish the amount of bone loss during GnRH-a therapy. Several studies investigated the use of GnRH-a versus GnRH-a plus add back therapy [34]. Pain decreased significantly in both groups but the side effects were far less in the group that also had add back therapy. After 6 months of therapy, Moghissi [35] demonstrated a 4.1% decrease in BMD in the group that was given GnRH-a only compared with a 1.5% decrease in BMD in the group that received GnRH-a plus

hormone replacement therapy (HRT) (.625 mg conjugated estrogen plus 5 mg MPA). Although BMD seemed to recover to a level that was similar to that found in the group that was given HRT 6 months after termination of therapy, both groups had lower lumbar, bone mineral density compared with pretreatment values [36].

Repetitive surgical therapy cannot be advocated for adolescents. The long duration of endometriosis makes them at risk for multiple surgeries that lead to adhesion formation and possible diminishment of fertility. The lack of correlation between stage of disease and degree of pain may impel the clinician to consider using a medical agent after excision or destruction of visible lesions. After laparoscopic operative surgery where lesions were excised or destroyed, patients were placed on GnRH-a or placebo for 6 months. More than half of the patients who received placebo needed further therapy within 2 years, whereas only one third of the patients who were given GnRH-a needed further therapy by 2 years [37]. Although this study showed a clear benefit to the use of GnRH-a following ablative therapy of endometriosis in adults, we reserve its use for adolescents with recurrence or failure of response to surgery or other medical therapies. We attempt to delay use of GnRH-a therapy until the later teen years when a significant increase in bone density has already occurred.

Surgical therapy

Only conservative treatment, whereby the reproductive organs are conserved, is indicated in adolescents. Careful attention to preservation of the ovarian cortex must be given; microsurgical skills must be used, as well as adhesion barriers, in an attempt to minimize adhesion formation. There was only one prospective, randomized trial that compared laparoscopic surgical removal of endometriotic implants with placebo treatment [38]. Seventy-four women with endometriosis were randomly assigned to either laser ablation of endometriotic lesions and laparoscopic uterosacral nerve ablation (LUNA) or expectant management laparoscopy at the time of diagnostic laparoscopy. The patients were blinded to the type of procedure they had undergone. At 3 months, equivalent pain relief was noted in the two groups. At six months, 62.5% of the treated group reported improved pain scores compared with 22.6% of the group that was not treated. Among patients in the former group, more than 90% continued to experience decreased pain at 1-year duration [39]. Unfortunately, pain response to surgical ablation of endometriosis was poorest in patients with stage I endometriosis. Only 38% of patients with stage I endometriosis noted an improvement of their symptoms [38]. As discussed earlier, this is the most common stage of endometriosis in adolescents.

Because the role of presacral neurectomy and LUNA, as an adjunct to surgical removal of endometriosis are not clearly defined in the literature [40,41], we do not advocate the use of these procedures on adolescents. There is no documentation in the literature to support a superior method of endometrial implant destruction. We believe that laser ablation, electrocautery, and excision of endometrial implants lead to similar end results.

Recurrence

It is very difficult to determine the exact rate of endometriosis recurrence. Endometriosis is not always a progressive disease [42]. Sutton et al's [39] follow up study showed disease progression in 29% of patients, disease regression in 29% of patients, and static disease in 42% of the symptomatic controls who had only received a diagnostic laparoscopy and expectant management. Conversely, neither medical nor surgical therapy will permanently eradicate endometriosis. Various investigators reported rates of recurrence ranging from 16% to 52% [43]. These differing rates may be the result of different treatments, different methods of diagnosing recurrence, and different duration of follow-up. Although some investigators suggested that the severity of the disease and the initial ASRM score are not predictive of the recurrence of endometriosis [44], others, such as Waller and Shaw [32], showed that women with higher stage disease are more likely to present with recurrence. Although the low stage of disease in the adolescent may make her at less risk of recurrence, the long duration of follow-up may make her at increased risk. The natural history of an adolescent who is diagnosed with stage I endometriosis is unknown. Long-term studies, in which the patients are followed over the next 3 to 4 decades, are necessary to be able to properly advise the adolescents and their parents about their likely outcome.

Follow-up

Because endometriosis can be a life-long disease, careful follow-up of the adolescents after surgical diagnosis and treatment is important. The findings are clearly reviewed with the patient and she is requested to return every 3 to 6 months. During this time her symptoms are monitored closely and she is educated about the possible, long-term nature of endometriosis and the need to minimize the number of pelvic surgeries. Concerns about fertility and quality of

Table 1
Differential diagnosis of pelvic pain

Gynecologic	Endometriosis
	Pelvic inflammatory disease
	Ovarian cysts, rupture, torsion, hemorrhage
	Mullerian anomalies
Gastrointestinal	Eating disorders
Urological	Lactose intolerance, malabsorption, chronic constipation, irritable bowel syndrome, Crohn's disease, ulcerative colitis, pancreatitis
	Urinary tract interstitial cystitis
	Ureteral calculus
Musculoskeletal	Abdominal wall trigger points
	Vulvodynia and vaginismus
Psychosexual	Sexual or physical abuse
	Drug abuse
	Psychogenic pain (eg, depression)

life are addressed. Unless contraindicated, most patients are placed on OCP after surgery. If the patient does not respond to surgery or has recurrence of symptoms, other modes of long-term, medical therapy are considered and an investigation into other causes of pelvic pain is warranted (Table 1). The use of gastroenterology, psychology, and urology disciplines ensures appropriate evaluation of such patients for coexisting diseases and optimizes their care.

Summary

Endometriosis is a cause of chronic, pelvic pain in adolescents. Lack of response to NSAIDS and OCPs should prompt further investigation and subsequent treatment. The goal of therapy is to minimize pelvic pain and dysmenorrhea primarily through long-term, medical therapy. Surgical intervention is principally indicated to establish a diagnosis. The poor response to surgical therapy negates the need for repetitive or radical surgery. Much patience and care should be directed toward these patients to provide them with an understanding of their disease and to help enhance the quality of their life.

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Controversies in adolescent hormonal contraception

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Sexually active adolescents in the United States are at high risk of unintended pregnancy. Recent trends show decreasing rates of pregnancy in this group, but rates still exceed those in other developed countries [1]. Relatively lower use of effective hormonal contraception and emergency contraception is an important contributing factor. Three areas of controversy regarding the provision of hormonal contraception and emergency contraception are discussed herein. Such controversies currently affect how these services are provided to adolescents in the Unites States.

Side effects of oral contraceptives

Oral contraceptives are a safe and effective method of contraception for adolescents [2]. Oral contraceptive use is associated with health benefits that are especially important during adolescence, including effective treatment for acne and menstrual cycle irregularity, a decreased risk of pelvic inflammatory disease and functional ovarian cysts, and possibly decreased dysmenorrhea. Nevertheless, a minority of sexually active teenagers use oral contraceptives, and very few teenagers use other effective hormonal methods such as injectables or implants. The most recent cycle of the National Survey of Family Growth in 1995 reported that 44% of persons currently using contraception aged 15 to 19 years used oral contraceptives; of those persons ever having intercourse, 52% had ever used oral contraceptives. Nineteen percent of sexually active teens not seeking pregnancy reported using no contraceptive in the last 3 months [3].

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The side effects of oral contraceptives are the most commonly reported reason why adolescents and older women do not initiate their use. Although large representative studies in adolescents have not been conducted, small studies using convenience samples have found that teenagers believe oral contraceptives cause side effects. At a Canadian family planning clinic, 54% of teenagers reported hearing that oral contraceptives cause weight gain, as well as nausea (23%), headaches (17%), and emotional changes (15%) [4]. In a study of 14- to 19-year-old females attending a San Francisco adolescent clinic, persons who believed that oral contraceptives affected physical appearance were less likely to intend to use oral contraceptives and less likely to start this medication than were persons who did not believe that oral contraceptives affected appearance [5]. A prospective study at a Michigan family planning clinic (62% teenagers) found that, after 1 year, 10% of those intending to use oral contraceptives never started [6].

Among persons who do take oral contraceptives, discontinuation rates are consistently high in diverse populations, including adolescents. A national prospective cohort study of 1657 new oral contraceptive users in the United States found that 15% discontinued the medication by 2 months; by 6 months, more than 30% had discontinued the medication. The proportion of adolescents included was not specified [7]. Smaller studies of adolescent populations have reported short-term discontinuation rates ranging from 30% to 50% [8].

Side effects are the most commonly reported reason why adolescents and older women discontinue oral contraceptive use. Discontinuation has been studied in larger more representative samples of oral contraceptive users than noninitiation. In the prospective cohort study by Rosenburg and Waugh, 37% of oral contraceptive users discontinued their use because of bleeding irregularities, nausea, weight gain, mood changes, breast tenderness, and headaches (proportion of adolescents not reported) [9]. A survey of 6676 European oral contraceptive users (19% aged 16–19 years) found that the side effects were the most frequent reasons given for discontinuation. Persons who experienced nausea, bleeding, breast tenderness, mood changes, hair growth, weight gain, and headaches were more like to discontinue than persons who did not report these effects [7]. A smaller study of a diverse population of adolescents in the United States found that oral contraceptive discontinuation at 3 months and 1 year was associated with concern about the side effects before starting oral contraceptives and the occurrence of side effects after starting [8].

Not starting and discontinuing effective methods of hormonal contraception such as oral contraceptives has a tremendous impact on adolescent pregnancy rates in the United States. US teenagers are less likely to use oral contraceptives, more likely to become pregnant, and more likely to become mothers than are teenagers in comparably developed countries [1]. To improve oral contraceptive initiation and compliance, practitioners and pharmaceutical researchers have suggested strategies that address the side effects. Many experts recommend counseling users to anticipate the side effects of oral contraceptives as a way to improve compliance [5,7]; however, no study has demonstrated that such counseling actually increases compliance. New oral contraceptive formulations are developed with lower doses

of hormones to decrease side effects and improve compliance. These strategies assume that the negative effects experienced during oral contraceptive use are caused by oral contraceptives. Is there good evidence to support this assumption?

With the use of any medication, two types of negative side effects can occur. First, side effects can occur that can be explained by the medication's pharmacologic action (these effects are usually predictable and dose dependent). Second, nonspecific effects can occur that cannot be explained by a clear physiologic mechanism. With the use of oral contraceptives, thrombosis is an example of the former effect and emotional lability an example of the latter. Data from studies involving many types of medications and patients indicate that an important proportion of negative side effects are explained by nonspecific, patient-related factors other than the pharmacologic actions of drugs.

In a recent review, Barsky et al outlined two mechanisms by which nonspecific side effects can become attributed to medication use [10]. First, negative physical feelings are common. Reidenberg and Lowenthal found that, among healthy persons not taking any medication, 14% reported headache, 23% drowsiness, 5% dizziness, and only 19% no symptoms during the previous 3 days [11]. Users may perceive that such pre-existing feelings are caused by new medications. For example, a woman who usually experiences breast tenderness that continues after starting oral contraceptives may attribute the breast tenderness to oral contraceptive use. Second, common health problems can be attributed to medication use because, by chance, they develop during that medication's use. For example, a woman in whom depression develops because of social circumstances occurring during oral contraceptive use might attribute the depression to the oral contraceptives.

Several factors influence the incidence of nonspecific negative side effects of medication. Patients who learn to expect distressing side effects are more likely to experience them. In one trial, more gastrointestinal side effects were reported by subjects who were told that an experimental drug had gastrointestinal effects than by subjects who were not told of this effect [12]. Patients who are anxious, depressed, or prone to somatization are also more likely to experience side effects to active and placebo medications [11]. No studies have examined how these factors affect the incidence of nonspecific negative side effects in oral contraceptive users.

Only by using a placebo control group can one determine the proportion of negative effects owing to pharmacologic action. If a drug causes a side effect, the rate of this event in the active drug group must exceed the rate of this effect in the placebo group. A small number of well-conducted, placebo-controlled oral contraceptive studies provide good evidence to evaluate whether oral contraceptives cause the side effects often attributed to them (Table 1). These studies have evaluated high-dose pills no longer in use [13] and contemporary low-dose pills [14], including one with the lowest currently available estrogen dose [15]. Only one of these trials was designed to examine the side effects of oral contraceptives as a primary outcome measure [13].

The results of these trials are summarized in Table 2. All of the studies included some adolescents, but the proportions were not specified. Goldzieher et al compared several pills with placebo. Data listed in the table from Gold-

Table 1
Randomized, placebo-controlled oral contraceptive trials

Author, year	Main outcome	Number of subjects	Oral contraceptive type	Age (years)	Side effect ascertainment
Goldzieher et al, 1971	Oral contraceptive side effects	398	100 μg EE + 25 mg dimethisterone 100 μg EE + 1 mg ethynodiol diacetate 50 μg mestranol + 1 mg norethindrone 0.5 mg chlormadinone acetate	—	Interview, list
Redmond et al, 1997, 1999	Acne	507	35 μg EE + triphasic norgestimate	28, 15–49	Interview, open-ended
Thiboutot, Coney 2001, 2001	Acne	721	20 μg EE + 100 μg levonorgestrel	28, 14–50	Diary; interview, open-ended.
Davis et al, 2000	DUB	201	35 μg EE + triphasic norgestimate	29, 15–50	Interview, open-ended
Lucky et al, 1997	Acne	257	35 μg EE + triphasic norgestimate	15–49	Interview, open-ended

Abbreviations: DUB, dysfunctional uterine bleeding; EE, ethinyl estradiol.

zieher's study are for the comparison that showed the greatest difference between oral contraceptives and placebo, that is, the highest dose pill (100 μg of ethinyl estradiol plus 25 mg of dimethisterone) during the first cycle of use. Goldzieher's data probably give the highest possible estimate of oral contraceptive side effects for two reasons. First, the oral contraceptives studied provided much higher doses than the amounts in currently used pills (five times the estrogen given in the study by Coney et al). Second, Goldzieher and colleagues specifically asked whether

Table 2
Reported rates of side effects

	Goldzieher et al		Redmond et al		Coney et al	
	COC	Placebo	COC	Placebo	COC	Placebo
Nausea	22%	9%	11%	9%	12%	10%
Vomiting	15%	3%	4%	3%	2%	1%
Headache	15%	15%	18%	20%	32%	30%
Weight gain	—	—	2%	2%	3%	2%
Breast pain	10%	6%	9%	5%	4%	3%
Breast enlargement	—	—	3%	2%	—	—
Abdominal pain	9%	4%	6%	4%	—	—
Back pain	—	—	6%	3%	—	—
Emotions labile	—	—	3%	0.5%	—	—
Nervousness	16%	16%	—	—	—	—
Depression	8%	5%	—	—	—	—
Low libido	—	—	0.5%	0%	—	—

Abbreviation: COC, combined oral contraceptive.

subjects experienced any of a list of effects believed to be related to oral contraceptive use, whereas the other studies used open-ended questions.

Other than nausea and vomiting in the groups using the highest dose oral contraceptive, common oral contraceptive side effects were reported by similar numbers of women in the oral contraceptive groups and placebo groups. Interestingly, by cycle three, even in the highest dose oral contraceptive users there was no difference in nausea or vomiting when these subjects were compared with the placebo group. In the trials by Davis and Lucky, individual side-effect rates were not reported, but the researchers stated that the incidence of adverse events was low and comparable in both groups [16,17]. The two studies comparing one oral contraceptive with placebo included enough subjects so that even small differences in the rate of side effects (probably smaller than would be clinically important) would be detected statistically. For example, either study would have 95% power to detect a difference of 15% versus 5% in any side effect in the oral contraceptive group versus the placebo group. Discontinuation rates because of side effects were also similar in the oral contraceptive and placebo groups in the studies using contemporary pills.

To adolescents, weight gain may be the most important possible side effect of oral contraceptives [4]. Unlike subjective experiences, such as nausea or breast tenderness, weight can be measured easily and accurately during clinical trials. Two of the studies summarized in Table 1 collected data on perceived weight gain [14,15], and two collected information on actual weight changes [13,15]. As true for other side effects, there was no difference in the rates of perceived weight gain between the oral contraceptive and placebo groups. Recorded weight also showed similar changes in the placebo and oral contraceptive groups. In the high-dose pill trial, most subjects' weight did not change over four cycles, weight gain was more likely than weight loss, and weight gain of more than 5 pounds was similar in the placebo and pill groups [13]. In the low-dose pill trial, small increases in weight were as likely as no weight change, and equal proportions of subjects in the oral contraceptive and placebo groups had no change, an increase, or a decrease in weight over six cycles [15].

Taken together, these studies provide no evidence to support the commonly held belief that contemporary oral contraceptives cause "hormonally related side effects," such as nausea, vomiting, weight gain, breast changes, or emotional changes. Nevertheless, oral contraceptive users expect negative effects, and, when these effects occur for whatever reason, these women discontinue oral contraceptive use. Evidence from other areas of medicine suggests that teaching patients to expect side effects increases the likelihood that such side effects will occur, especially among persons susceptible to experiencing nonspecific drug reactions. Research has yet to examine the specific use of oral contraceptives; however, it seems likely that oral contraceptive labeling and clinician- and media-driven messages about the expected side effects of oral contraceptives could paradoxically contribute to their discontinuation rather than increase compliance.

Is it time to change counseling regarding oral contraceptives? Clinical trials should address how positive and negative information about oral contraceptives

affects compliance. Health care providers need to convey more current, evidence-based messages to patients. A national survey of more than 350 obstetricians–gynecologists and nurse practitioners found that nearly half associated weight gain with oral contraceptive use [18]. Changing beliefs about the side effects of oral contraceptives among health care providers is not the only answer. According to the American Academy of Pediatrics, adolescents spend more than 40 hours each week using television, music, and the Internet [19]. A bigger challenge will be addressing media messages to adolescents that emphasize the health risks and negative effects of oral contraceptives more than the health benefits [20].

Possible adverse effects of long-acting progestin injectables on bone health

Depot medroxyprogesterone acetate (DMPA, Depo-Provera) is in some ways an ideal contraceptive for adolescents. The 12- to 14-week dosing schedule allows flexibility and minimal maintenance, the failure rate is extremely low, and the method is reversible and safe for women who have contraindications to estrogen-containing contraceptives [21]. DMPA exerts its contraceptive effect by inhibiting the secretion of pituitary gonadotropins, which suppresses ovulation and endometrial proliferation [21]. In some users, ovarian suppression leads to at least partial estrogen deficiency [22,23]. As use of DMPA becomes more prevalent, concerns about bone resorption from hypoestrogenism and osteoporosis in long-term users have emerged.

Estrogen status and bone mineral density (BMD) are especially important in adolescents. Early in the second decade, peak bone mass is reached in women in most anatomic sites [24,25]. Peak BMD is a critical determinant of the risk for osteoporotic fractures later in life, and primary prevention of osteoporosis can occur during adolescence. The determinants of peak bone density include genetic factors, exercise, smoking, diet, calcium intake, race, body weight, and estrogen status. A family history of osteoporosis and estrogen status seem to be the most important of these factors. Because family history is not modifiable, ensuring adequate estrogen levels is an important preventive measure that can be taken against later osteoporosis. Accordingly, several issues are presented: (1) Is DMPA use associated with the loss of BMD? (2) Is this loss clinically significant? (3) Is this loss reversible after termination of treatment? (4) Does the effect differ between adolescents and adult women?

Several studies have addressed the question of DMPA and bone loss using a variety of designs and populations. The first concerning study was performed by Cundy et al [26] who in 1991 reported significantly decreased BMD at the femoral neck and lumbar spine in 30 long-term DMPA users. The mean reduction was 7.5% in the lumbar spine and 6.6% in the femoral neck in a comparison with 30 premenopausal controls. This loss was not sufficient to put the DMPA users at higher risk of imminent fracture; however, extrapolation based on their age-specific BMD predicted a 30% to 100% increase in their lifetime risk for

osteoporotic fracture [27], assuming no resolution of the bone loss after stopping treatment. The women in this study ranged in age from 25 to 51 years, and the median DMPA use was 10 years. Four times as many DMPA users were smokers when compared with the premenopausal controls, a factor also known to affect BMD.

Following this report, additional studies in New Zealand, North and South America, Europe, and Asia evaluated the question of BMD in current DMPA users [28–44]. Banks et al have summarized current epidemiologic evidence on DMPA use and BMD [45]. Using available evidence from eight cross-sectional studies of very different populations, they calculated a *z* score for each study by determining the difference between the BMD of DMPA users and nonusers in that study and dividing that figure by the standard deviation of the nonusers. A *z* score of -1 indicated that the mean BMD of the DMPA users in that study was one standard deviation lower than that of nonusers. Ninety-five percent confidence intervals were also calculated for each study. Because of considerable heterogeneity between the studies, Banks and colleagues could not generate a summary *z* score; however, all eight studies demonstrated lower BMD with current DMPA use in a comparison with controls in at least one anatomic region examined. Most of the *z* scores were between 0 and -0.5; none was less than -1.0. Naessen et al [29], Cromer et al [30], Merki-Feld et al [41], and Berenson et al [44] each prospectively evaluated BMD loss with DMPA use. The sample size in these studies ranged from 11 to 36 DMPA users. Two of the studies [30,44] compared the BMD change in DMPA users with the BMD change in controls not using hormonal contraception. These two studies found small losses of BMD that were significantly different from the findings in controls, whereas the other two studies found no significant change in BMD over 6 months [29] or 12 months [41].

In 1994 Cundy et al followed up their study of DMPA current users with an evaluation of BMD recovery after discontinuation of DMPA [28]. They prospectively evaluated 14 women who had used DMPA for at least 3 years, measuring baseline and 12-month postdrug BMD. In eight women, a second follow-up measurement was obtained at 24 months. These data were compared with the findings in a group of 22 women who continued to use DMPA and a group of 18 women who had never used DMPA. Reassuringly, the results indicated almost complete recovery of BMD 2 years after discontinuation. Petitti et al [40] and Orr-Walker et al [35] compared past users with nonusers in a cross-sectional fashion, finding no difference in BMD between these groups.

Theoretically, the long-term bone health risks for adolescent DMPA users may be higher than the risks for adult women. The small studies in adolescents published thus far have found decreases in BMD associated with DMPA use. The population-based, cross-sectional study of 457 women by Scholes et al [38], comprising 183 DMPA users and 274 controls, was large enough to stratify by age. Although the overall mean BMD decrease in DMPA users when compared with nonusers was 2.5% at the spine and 2.2% at the femoral neck, the 18- to 21-year-old age group showed a 9.4% difference at the spine and similar

differences at other anatomic sites. In this age group, there were 48 DMPA users and 62 nonusers. Although there were significant baseline differences between users and nonusers, the difference in BMD between the groups persisted after controlling for these factors in the analysis. In all other age groups, there were no significant differences in mean BMD at any anatomic site.

Cundy et al [34] extended their original study of 30 DMPA users to include 200 users and 300 controls. Twenty-six of the 200 DMPA users began use before age 21 years. This group had the greatest difference from controls in lumbar spine BMD. Of these subjects, 14 had used DMPA for over 15 years and had a mean z score of -1.20. Twelve of the adolescent starters had used DMPA for less than 15 years and had a mean z score of -0.87. Further analysis demonstrated significant effects on bone density related to long duration of use and early initiation, again suggesting that DMPA use before the achievement of peak BMD may have a different impact than use by adult women.

A longitudinal study of DMPA use and BMD in adolescent girls was conducted by Cromer et al [30]. They evaluated a convenience sample of postmenarcheal girls between the ages of 12 and 21 years who had previously used no hormonal contraceptives. All of the subjects were seen for medical care and chose a contraceptive method if appropriate. Baseline BMD measurements were obtained on all subjects. A total of 48 girls composed the study sample at 1 year. Seventeen of these girls were abstaining from sexual intercourse or using barrier contraceptives (control group), and 31 girls were using a hormonal method of contraception. These methods included levonorgestrel implants (Norplant) (n = 7), DMPA (n = 15), and oral contraceptives (n = 9). Three implant users, eight DMPA users, and four controls were still available for BMD evaluation at 2 years. Baseline BMD measurements among the four groups did not differ. After 1 year, DMPA users had a 1.53% decrease in BMD compared with a 2.46% increase in implant users, a 1.52% increase in oral contraceptive users, and a 2.85% increase among controls. The difference between the BMD change in DMPA users and controls was statistically significant. At 2 years, although the groups were small, the mean BMD loss among DMPA users was 3.12% versus a 9.49% increase among controls. Changes in bone density were not explained by a range of background variables examined.

More definitive answers about the effect of DMPA on short- and long-term bone health will be forthcoming from several studies currently in progress; however, the data obtained thus far are suggestive. DMPA is associated with a measurable decline in BMD when compared with the BMD in nonusers in cross-sectional studies and in longitudinal measurements in some prospective studies. This loss seems to be less than one standard deviation. Several studies indicate that the loss is reversible. Although available data on adolescents are scant, they indicate that this group may be especially vulnerable to BMD loss. Furthermore, it is not known whether bone loss before achieving peak bone density is recoverable, or to what extent the loss impacts the later risk of osteoporotic fracture. It is well known that risk factors cluster. Early sexual activity, smoking, alcohol use, and poor diet choices occur together, and adolescents using DMPA

are more likely to demonstrate other high-risk behaviors [46]. The physical, social, and psychologic risks of teen pregnancy should not be underestimated. Until the results of larger, well-controlled studies are available, definitive recommendations regarding DMPA use by teenagers cannot be made. Special consideration should be given regarding DMPA use by persons already at highest risk for low BMD, such as thin competitive athletes and dancers, smokers, and teenagers with a family history of osteoporosis [47]. Increased calcium intake, weight-bearing exercise, and smoking avoidance can add as much as 5% to 10% to peak BMD [48] and are worthwhile interventions for all teenagers.

Issues regarding emergency contraception available to teenagers without a prescription

Hormonal postcoital or ''emergency'' contraception has been available since the 1970s, when Yuzpe and Lancee described a regimen of combined ethinyl estradiol and levonorgestrel oral contraceptive for this purpose [49]. Emergency contraception is estimated to reduce the risk of pregnancy by at least 74% when taken within 72 hours of unprotected intercourse and by up to 95% if taken within the first 24 hours [50,51]. Emergency contraception may be used to prevent unintended pregnancy owing to miscalculation of cycle day, missed oral contraceptive pills, an out-of-position diaphragm or female condom, a broken or displaced male condom, or when no method is no used. Although several European countries have had dedicated emergency contraception products available for some time, until recently, US health care providers were required to assemble emergency contraception regimens from various combinations of oral contraceptive tablets. The first hormonal combination marketed as an emergency contraception in the United States became available in 1998. The combined estrogen and progestin emergency contraception kit (Preven) contains four tablets of ethinyl estradiol, 50 μg, and levonorgestrel, 250 μg each, and instructions to take two tablets within 72 hours of unprotected sex, repeating the dose 12 hours later. A progestin-only product (Plan B) became available in 2000 and includes two tablets of levonorgestrel, 750 μg each, to be taken 12 hours apart. Both of the products are available in the United States by prescription only.

Although access to emergency contraception is important for all sexually active reproductive-aged women, it is especially important for adolescents. Data from the 1995 National Survey of Family Growth demonstrated that adolescents were significantly less likely to use effective contraceptive methods than were older women, were more likely to use methods sporadically, and were more likely to be contraceptive nonusers [52]. These findings may be explained by infrequent, unanticipated, or irregular sexual activity patterns [52]; less awareness of pregnancy risk [53]; or ambivalence about sexuality. Furthermore, adolescents face obstacles in obtaining the necessary medical consultation to obtain emergency contraception. They may be less likely to have a regular source of care or may be uncomfortable discussing contraceptive issues with their pediatrician or

family physician. A clinic visit requires missing school or work and making excuses to parents or teachers. It is estimated that two thirds of all unintended pregnancies could be avoided each year if emergency contraception were better used. An estimated 78% of teen pregnancies are unintended [54], a finding with potential major effect on adolescent health.

Emergency contraception can be effective in pregnancy prevention up to 5 days after unprotected intercourse, but its effectiveness is inversely related to the time elapsed before initiating the medication [51]. Because time is of the essence, it has been proposed that one barrier to the use of emergency contraception be removed by dropping the requirement for medical consultation. Proposals include access through a pharmacist, advance provision of prescriptions or medication, or making the treatment available over the counter [55,56]. Nevertheless, direct access for adolescents raises several concerns.

The first concern if emergency contraception were available over the counter is that women would not receive proper education in regard to timing, dosing, and the use of repeated courses. Currently, despite educational efforts, confusion regarding the proper time to use emergency contraception is still prevalent in the United States [57–61]. Many teenagers who are aware of emergency contraception may wait until a missed menstrual period before asking about it. Health care providers are also unclear about the proper use of emergency contraception. In a survey of health care providers from the departments of obstetrics and gynecology, primary care, emergency medicine, and pediatrics at 13 San Diego County Kaiser Permanente medical offices, 42% of respondents provided the correct answer in regards to when the first dose must be taken, and 57% knew the correct interval between the two doses [62]. Requiring a prescription for emergency contraception may not guarantee correct use. Regardless of whether it is available over the counter, without increased patient education, emergency contraception may be less effective in reducing unintended pregnancy than anticipated.

If women use emergency contraception incorrectly, is it unsafe? The hormones in emergency contraception are the same agents used by millions of women worldwide for the last 40 years in oral contraceptive regimens. The incidence of serious complications with oral contraceptives is very low, even with long use. A high-dose exposure over a 12-hour period is unlikely to present a serious health risk. No changes in clotting factors have been demonstrated with emergency contraception [63]. An international study of almost 2000 women randomized to combination versus levonorgestrel emergency contraception [51] found only nuisance side effects, such as nausea, headache, and fatigue. Pregnancy is a contraindication to emergency contraception use because the method will be ineffective, but extensive research has shown no teratogenic effects [64]; therefore, concerns regarding incorrect use are most properly addressed by increased education and not by limiting access.

A second concern is that sexually active adolescents are at high risk for the acquisition of sexually transmitted disease (STD). Presentation to a clinic or physician for emergency contraception is an opportunity to screen and treat girls who, by definition, have had unprotected intercourse. In one small British study,

32.8% of emergency contraception requestors who were offered a sexual health screen accepted it. Of these subjects, 15.8% had an STD [65]. In a different population of 134 Swedish emergency contraception users, none were found to have a chlamydial infection [66]. Evaluation for STDs was also addressed among a US adolescent population with increased access to emergency contraception. The Washington State emergency contraception project educated and trained pharmacists to provide emergency contraception directly to women requesting it. A survey study performed in association with this project assessed the risk factors for adolescent girls using the service [67]. Forty-one percent of the adolescents who completed the survey indicated that they had a new or possibly non-monogamous partner; of these teenagers, 41% stated they had no intention of seeing a physician in the next month. In the same survey, 58% of respondents indicated they would see a physician when asked, "If you couldn't get emergency contraception from the pharmacist, what would you do?" Although there is a clear need for STD screening among young women seeking emergency contraception, it is not clear that restricting direct access to emergency contraception will fulfill this need.

Another significant concern about direct access to emergency contraception is that young women may be tempted to be less compliant with more effective methods of birth control. Several studies around the world have attempted to address this issue. The school health promotion study in Finland was designed to provide data on adolescent health behaviors. Conducted in 1996, the 52,700 respondents included 21,940 girls aged 14 to 18 years. Only 3% of the 14 to 15 year olds and 1.5% of the 18 year olds had no knowledge of emergency contraception. Two percent and 15% of girls in these age groups, respectively, had used emergency contraception. Of emergency contraception users, 64.6% had used it only once; 4.9% of girls reported using it three or more times [68]. Nonrepetitive use without an increase in the teen pregnancy rate indicates that emergency contraception has not replaced conventional methods of birth control in Finland. Furthermore, age-specific sexual experience rates have not changed since the introduction and easy availability of emergency contraception.

Glasier and Baird randomized 1083 women in Edinburgh, Scotland to receive an advance supply of emergency contraception and education in its use versus education alone [69]. The women in the advance supply group were more likely to use emergency contraception at least once during the 1-year study period (36% versus 14%, $P < 0.001$) but were not more likely to use emergency contraception repeatedly (12% versus 13%). The relative risk of unintended pregnancy in the advance provision group was 30% lower. A similar proportion in each group switched from barrier methods to oral contraceptives. The advance provision group's use of contraceptive methods was no different from use in the education-only group.

In the United States, Raine et al likewise allocated 263 women aged 16 to 24 years to receive either education and an advance supply of emergency contraception or education alone [70]. At follow-up 4 months later, women in the advance provision group were almost three times as likely to have used

emergency contraception when compared with women in the control group. Women in the advance provision group were also more likely to be using a less effective method of contraception (barrier versus hormonal) at the 4-month follow-up than were women in the education-only group. At baseline, women in the control group already were more likely to report consistent oral contraceptive and condom use than were women in the treatment group. Regardless, there was no significant increase in the proportion of women reporting unprotected sex or a decrease in consistent condom use in the advance provision group.

Ellertson et al randomly assigned 411 condom users in India to advance provision of emergency contraception versus education only [71]. Although both groups reported the same rate of unprotected intercourse, supply recipients were nearly twice as likely to have used emergency contraception. No woman used emergency contraception more than once, although the advance provision group had three regimens available. All of the women in the control group indicated they wished they had received supplies. It was concluded that easy access to emergency contraception encourages its use but does not promote more contraceptive risk taking.

Currently, access to emergency contraception for adolescents is very limited. Even for young women with knowledge of emergency contraception, the required medical consultation may be difficult to arrange on short notice. One attempt to remedy this situation was the establishment of an emergency contraception hotline consisting of a toll-free telephone number and Web site that provided the names and contact information of health care providers committed to providing emergency contraception. Trussell et al [72] found that when two female researchers called 200 providers listed on the hotline, only 76% of these attempts resulted in an appointment or telephone prescription within 72 hours. Meanwhile, despite advertising by various medical and public service organizations, knowledge remains poor. If emergency contraception were available by direct access, marketing efforts would certainly intensify, as they have for other medications that have made the transition to over-the-counter availability. Although concern for improper use persists, in fact, women who are provided education on the method use the method correctly, and incorrect use does not pose a health risk beyond unintended pregnancy. Although there is definitely an unmet need for STD screening among adolescents, withholding access to emergency contraception may not be an appropriate or effective way to remedy this problem. Several large and small-scale studies among various populations indicate that direct access to emergency contraception does not lull women into taking chances with more effective contraception.

The provision of contraceptive care to adolescents requires special consideration of their unique medical and lifestyle needs. Many young women discontinue oral contraceptives owing to perceived side effects; however, current evidence suggests that most of these symptoms, ranging from headache to weight gain, are not caused by the oral contraceptives. DMPA provides effective pregnancy protection that is independent of daily or incident-specific compliance, but questions regarding long-term effects on bone health remain unanswered. Although teen-

agers are likely to benefit from increased access to emergency contraception, over-the-counter labeling of emergency contraception remains controversial.

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