

Delayed Puberty

David S. Rosen, MD,
MPH,* and Carol Foster,
MD†

Objectives After completing this article, readers should be able to:

1. Delineate the differential diagnosis of delayed puberty.
2. Compare the prevalence of constitutional delay of puberty with that of other causes of pubertal delay.
3. Describe the typical presentation and natural history of constitutional delay of puberty.
4. Describe the indications for and initial evaluation of pubertal delay.
5. Recognize the psychosocial sequelae of severe pubertal delay.

Introduction

Development and maturation of the reproductive system begins in fetal life and is a surprisingly active process throughout the first postnatal months. The reproductive system becomes quiescent during childhood until its reactivation triggers pubertal development. Puberty begins with increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, increased pituitary responsiveness to GnRH, increased secretion of gonadotropins, gonadal maturation, and increasing production of sex steroids. Increased concentrations of sex steroids induce the development of secondary sexual characteristics, acceleration of growth, and ultimate fertility. Factors that determine the timing of pubertal onset remain poorly understood and the subject of intense investigation, but general health, nutrition, and genetic factors all are known to contribute.

The diagnostic criteria for pubertal delay are based roughly on statistical norms (ie, delay of more than 2 to 3 standard deviations from the mean age of pubertal onset), but in fact they are somewhat arbitrary. Puberty is considered to be clinically delayed if sexual maturation has not become apparent by age 14 years in boys or age 13 years in girls. This clinical diagnosis also is made in the absence of menarche by age 16 years or in the absence of menarche within 5 years of pubertal onset. Using these criteria, approximately 2.5% of healthy adolescents will be identified as having pubertal delay. Most are boys. After evaluation, the majority of these adolescents will be found to have no pathology; rather, onset of their otherwise normal puberty simply is sufficiently late or slow relative to that of their peers to have triggered concern and evaluation. When puberty does begin, it is entirely normal. Some adolescents have a variety of other causes to explain pubertal delay (Table), and with careful evaluation, most are diagnosed accurately.

Differential Diagnosis

Constitutional Delay

In constitutional delay of puberty, the normal prepubertal growth nadir is protracted. Presumably, the pubertal increase of pulsatile GnRH secretion is slow to develop, which delays pubertal levels of sex steroid secretion and their developmental effects on secondary sexual characteristics and growth hormone production. The prototypic patient who has constitutional delay of puberty is a 14- or 15-year-old boy who presents after most of his peers have begun puberty. Boys present far more often than girls because short stature and sexual immaturity extract a higher psychosocial price in males than in females. In many cases, delay of puberty is superimposed on constitutional short stature, exaggerating the effects of the delay.

*Editorial Board.

†Professor of Pediatrics and Communicable Diseases; Director, Division of Pediatric Endocrinology, University of Michigan Medical School, Ann Arbor, MI.

Table. Differential Diagnosis of Delayed Puberty

Increased Serum Gonadotropins

- Turner syndrome (gonadal dysgenesis)
- Klinefelter syndrome
- Bilateral gonadal failure
 - Primary testicular failure
 - Anorchia ("vanishing testes syndrome")
 - Premature ovarian failure
 - Resistant ovary syndromes
 - Irradiation
 - Cytotoxic therapy
 - Trauma
 - Infections
 - Castration

Normal or Low Serum Gonadotropins

- Constitutional delay of puberty
- Hypothalamic dysfunction
 - Malnutrition
 - Strenuous exercise
 - Chronic illness
 - Eating disorders
 - Severe obesity
 - Central nervous system tumors
- Hypopituitarism
 - Panhypopituitarism
 - Isolated gonadotropin deficiency
 - Kallman syndrome (with anosmia)
 - Isolated growth hormone deficiency
- Hypothyroidism
- Hyperprolactinemia
 - Pituitary adenoma
 - Drug-associated

Other Conditions

- Anatomic abnormalities
- Prader-Willi syndrome
- Lawrence-Moon syndrome
- Bardet-Biedl syndrome
- Bloom syndrome
- LEOPARD syndrome
- Ataxia-telangiectasia syndrome
- Cerebrohepato renal syndrome
- Noonan syndrome
- Androgen resistance
- Steroidogenic enzyme defects
 - Cholesterol desmolase complex deficiency
 - 3- β -hydroxysteroid dehydrogenase deficiency
 - 17- α -hydroxylase deficiency
 - C17,20-desmolase deficiency
 - 17- β -hydroxysteroid oxidoreductase deficiency

History may reveal similarly delayed puberty in the patient's parents or siblings. Findings on physical examination are unremarkable except possibly for early signs of puberty unnoticed by the patient. Laboratory evaluation results are normal, although bone age is delayed and consistent with the extent of pubertal maturation.

The outcome of isolated constitutional delay of puberty is excellent; neither sexual maturity nor final adult height is affected by the timing of pubertal onset. However, when constitutional delay of puberty is superimposed on constitutional short stature, final height will be short. Resolving the relative effects of these factors in final height has been difficult in the studies performed to date.

Chronic Illness

Chronic illness may affect pubertal onset, tempo, and potential. The pathophysiology of pubertal delay in chronic illness is variable, frequently multifactorial, and in some cases, not well-established. Chronic illness may affect underlying genetic potential, disturb physiologic function, or limit adequate nutrition. Chronic use of glucocorticoids, cancer chemotherapy, other medications, or radiation therapy may have short- or long-term consequences for growth or sexual maturation.

Adolescents who have chronic conditions, about which they already are acutely self-conscious, deserve particularly close monitoring of their pubertal course to allow early detection of pubertal difficulties. Often, only reassurance that puberty ultimately will proceed and eventual development will be normal is all that is required. However, when more pathologic pubertal derangements are detected, they should be treated early to maximize the potential for catch-up. Nutrition should be a priority, especially in those conditions where it frequently is compromised (eg, inflammatory bowel disease, cystic fibrosis), with supplementation used where appropriate. The risks and benefits of proposed medications and therapies, especially their effects on growth and maturation, always should be considered. Other explanations for pubertal delay should be investigated when the disease process does not explain maturational insufficiency or delay adequately. Finally, hormone replacement or augmentation with exogenous sex steroids is appropriate in some settings, but it is not a substitute for aggressive management of the underlying condition.

Hypopituitarism

PANHYPOPITUITARISM (CONGENITAL OR ACQUIRED).

Delayed puberty is not a common presentation of panhypopituitarism; affected children typically present with

short stature earlier in childhood. Panhypopituitarism presenting in adolescence is usually due to idiopathic hypothalamic failure. However, other unusual central nervous system etiologies (eg, tumor, Langerhans cell histiocytosis) should be ruled out.

ISOLATED GONADOTROPIN DEFICIENCIES (KALLMAN SYNDROME). The syndromes of isolated gonadotropin deficiency (IGD) are heterogeneous in clinical presentation. They occur more frequently in boys than in girls and often are difficult to distinguish from constitutional delay. IGD in association with hyposmia or anosmia is known as Kallman syndrome. The KAL-1 gene encodes a protein that allows fetal GnRH neurons to migrate from the olfactory placode through the cribiform plate and into the hypothalamus. Deletion of the KAL-1 gene is associated with sensorineural deafness, kidney malformations, and pes cavus. Boys who have GnRH deficiency often have a small phallus and testes, but findings on history and physical examination may be entirely normal except for sexual immaturity. Delayed bone age is the only consistent laboratory finding.

Other Endocrinopathies

HYPOTHYROIDISM. Thyroid hormone is required for normal puberty. Its absence may delay the onset or retard the progress of pubertal maturation by interfering with gonadotropin secretion. Thyroid replacement therapy usually normalizes gonadotropin secretion and allows puberty to proceed normally.

HYPERPROLACTINEMIA. Hyperprolactinemia may cause primary or secondary amenorrhea, but it is an otherwise rare cause of delayed puberty. Elevated prolactin levels interfere with gonadotropin production and may be due to a functioning pituitary adenoma (prolactinoma) or related to use of prescribed or illicit drugs (eg, phenothiazines, cocaine). Measurement of serum prolactin is a useful part of the evaluation for amenorrhea or delayed puberty, even in the absence of galactorrhea, and always should be obtained in the presence of galactorrhea. Prolactinomas may not be visible on imaging studies of the brain, making diagnosis more difficult.

Bilateral Gonadal Failure

Bilateral gonadal failure is uncommon and is characterized by markedly elevated concentrations of serum gonadotropins. The most common causes of gonadal failure are congenital: Turner syndrome (gonadal dysgenesis) and Klinefelter syndrome. Other congenital

causes of gonadal failure and acquired bilateral gonadal failure are rare.

TURNER SYNDROME. Girls who have Turner syndrome have short stature, variable but incomplete puberty, primary amenorrhea, and characteristic congenital anomalies. Growth retardation is the most consistent characteristic and begins in utero. Rarely is a pubertal growth spurt seen. For some girls, the diagnosis will not be made until they present with pubertal insufficiency. Most girls who have Turner syndrome have primary ovarian failure that gives rise to markedly elevated levels of gonadotropins by adolescence, although variable sexual development still occurs. More than 50% of patients in one study had some breast development, and some pubic and axillary hair is typical for most patients. A minority of affected girls experience spontaneous menarche at an average age of 13.4 years, but most girls who have Turner syndrome require long-term estrogen replacement therapy.

KLINEFELTER SYNDROME. Klinefelter syndrome is relatively common. The genotype is typically 46,XXY, but genetic variability and mosaicism occur. Many affected boys are not identified until puberty or early adulthood. Often, some spontaneous pubertal development occurs, but testes become fibrotic and smaller as boys become older. Males who have Klinefelter syndrome present with small testicles and external genitalia and often have gynecomastia. Affected boys tend to be tall in childhood, and their tall stature sometimes delays diagnosis despite their pubertal immaturity. Borderline intellectual abilities or behavioral difficulties sometimes lead to diagnosis in childhood or may be appreciated in retrospect. In adolescence, young men who have Klinefelter syndrome present with small testicles and hypogonadism. Testosterone production is abnormally low, follicle-stimulating hormone values are high, and oligospermia or azospermia is seen.

ACQUIRED CAUSES OF GONADAL FAILURE. Iatrogenic gonadal failure may occur in the aftermath of chemotherapy, radiation therapy, or surgery. Acquired gonadal failure also may have traumatic, postinfectious, autoimmune, or metabolic causes. Mumps orchitis is the most common infectious cause of gonadal failure. Autoimmune oophoritis, a rare cause of ovarian failure, often is associated with Addison disease and other autoimmune endocrinopathies. In galactosemia, the effects of galactose or its metabolites on the prenatal or neonatal ovary

may cause delayed or deficient puberty in girls or may be a cause of menstrual dysfunction.

OTHER CONGENITAL SYNDROMES. Among patients who have complete androgen insensitivity, phenotypic females have the XY genotype and present with primary amenorrhea and sparse or absent pubic and axillary hair despite normal thelarche. Prader-Willi syndrome is associated with hypogonadism, short stature, and obesity in both males and females. Micropenis and bilateral cryptorchidism are characteristic of boys; hypoplasia of the labia majora and clitoris are seen in girls, who also frequently have delayed or absent menarche. Hypogonadotropic hypogonadism occurs in both the Laurence-Moon syndrome and the Bardet-Biedl syndrome. Boys who have Noonan syndrome have abnormal testes (cryptorchidism, atrophy, anorchia), and their sexual maturation is consistently delayed. Many have primary gonadal failure with no spontaneous puberty, and infertility is common.

In the “vanishing testes syndrome,” 46,XY karyotype and masculine-appearing genitalia are associated with absent testes and failure of puberty. Presumably, testicular atrophy or destruction occurred some time after fetal differentiation of the external genitalia. Patients who have “resistant ovaries syndrome” have a 46,XX karyotype and typically present with sexual immaturity and primary amenorrhea. Further evaluation reveals small ovaries with primordial follicles despite elevated gonadotropin concentrations. The pathophysiology is believed to be due to abnormalities in gonadotropin receptors or antibodies to these receptors.

A long list of other congenital disorders and syndromes may be associated with pubertal delay or failure. These include Bloom syndrome, LEOPARD syndrome, ataxia telangiectasia syndrome, and the cerebrohepato-renal syndrome. Enzyme defects in steroid synthesis (eg, cholesterol desmolase complex, 3-beta-hydroxysteroid dehydrogenase) also can lead to pubertal failure. Genetic males who have these disorders are born with ambiguous genitalia.

Hypogonadotropic Hypogonadism

Other conditions, including eating disorders, malnutrition, and excessive exercise, may cause hypogonadotropic hypogonadism that results in pubertal delay or insufficiency. Girls are affected more often than boys and typically present with primary or secondary amenorrhea. Girls who are competitive athletes have significantly later pubarche and menarche than their peers, with the delays proportional to the intensity of their training. Similarly, eating disorders can disrupt normal pubertal progress

profoundly. Weight gain usually corrects these abnormalities, although women who have eating disorders are at higher risk for menstrual irregularity independent of weight.

Congenital Anatomic Abnormalities

Congenital anomalies of the female reproductive tract usually present with delayed onset of menses despite normal development of secondary sexual characteristics. Congenital anomalies associated with the apparent absence of menses include imperforate hymen, vaginal atresia, or vaginal aplasia. Other girls present in the early teen years with cyclic abdominal pain as a result of a normally responsive endometrium and spillage of menstrual fluid into the pelvis (“concealed menarche”).

Evaluation of Pubertal Delay

The extensive differential diagnosis of delayed puberty requires a systematic and focused approach to evaluation. Anosmia, galactorrhea, or symptoms of hypothyroidism may suggest a specific diagnosis. A careful history can identify excessive exercise or symptoms of chronic illness or psychiatric disease. A positive family history for pubertal delay would support the diagnosis of constitutional delay of puberty. Careful measurement of growth and determination of sexual maturity are the initial steps in physical assessment. Early signs of sexual development, unnoticed by the patient, may eliminate the need for a costly evaluation. A careful physical examination can help to identify stigmata of unsuspected congenital syndromes.

Determination of serum gonadotropin levels will distinguish disorders of congenital or acquired gonadal failure from other causes of delayed puberty. By adolescence (bone age 10 to 12 y), gonadal failure consistently produces markedly elevated levels of serum gonadotropins. When these are present, findings from the history and physical examination will often point to the specific diagnosis. Chromosomal analysis is indicated to confirm clinical suspicion of gonadal dysgenesis or Klinefelter syndrome. On the other hand, when serum gonadotropins are normal or low, constitutional delay of puberty is the most frequent diagnosis. However, further laboratory evaluation may be required to exclude the possibility of occult chronic illness or endocrinopathy. Reasonable screening studies include a complete blood count, erythrocyte sedimentation rate, and measurement of serum prolactin and serum thyrotropin-stimulating hormone. Even when results of these studies are normal, IGD remains a possible diagnosis because no studies reliably distinguish IGD from constitutional delay (Figs. 1 and

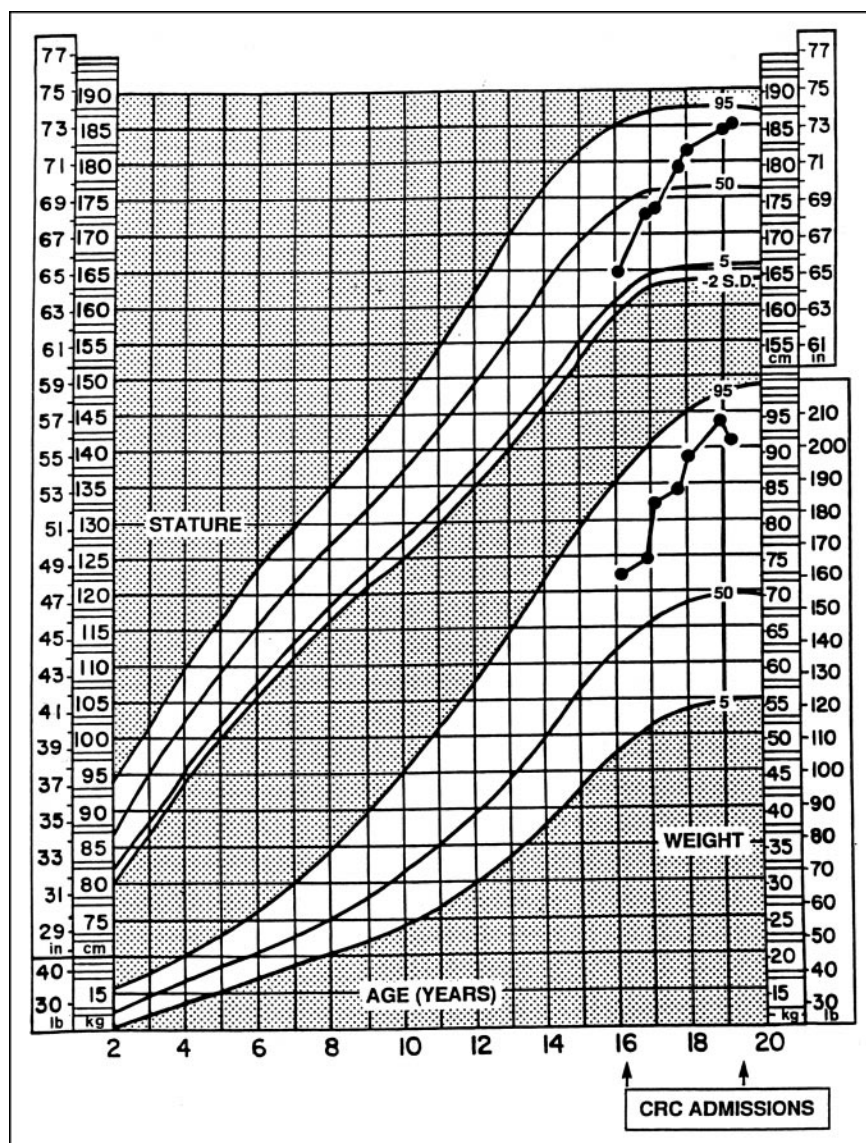


Figure 1. Growth chart for a patient who presented at age 16 years for pubertal delay. After evaluation, the patient was treated with depot testosterone for presumed isolated gonadotropin deficiency. Testicular development was seen at age 19 years, and testosterone was withheld. Pubertal development proceeded, and at final follow-up, height was 190.3 cm, external genitalia were fully developed, and the patient was attending college, dating, and demonstrating no psychosocial maladjustment.

2). Measurement of first morning urinary testosterone or stimulation testing using a GnRH agonist eventually may help to differentiate these conditions, but neither study currently is in broad general use.

Management

Ideally, management of pubertal delay should address the underlying cause if one can be identified. For patients

whose hypothalamic hypogonadism is related to exercise, eating disorder, or chronic illness, every effort should be made to effect changes in overall health and nutrition that will allow spontaneous puberty to proceed. Constitutional delay of puberty may be managed by reassurance alone, given our understanding that even striking delays will have no effect on final adult height or development (Fig. 1). Expectant management is more acceptable to families when clinicians can point out early signs of puberty that were not obvious to the patient. However, short-term hormonal therapy to “jump start” puberty may be appropriate when severe delay has led to psychosocial dysfunction.

Testosterone injections (eg, testosterone enanthate 100 mg intramuscularly administered monthly for 6 mo) are used for boys whose pubertal development already has begun. For boys who have not yet begun puberty, oral oxandrolone can be used at a starting dose of 1.25 mg daily. Such treatment should be monitored by specialists familiar with the potential side effects, including hepatic peliosis and premature epiphyseal closure. All boys treated with sex steroids should be monitored at 3- to 6-month intervals to assess response to treatment and skeletal maturation. Treatment is discontinued when it is expected that endogenous hormone production is established.

Patients who have gonadotropin deficiency or hypogonadism require lifelong replacement with sex steroids and should be managed in consultation with a pediatric endocrinologist. Testosterone supplementation is begun in boys at approximately age 12 years. It may be administered by injection, transdermal patch, or topical gel. Doses initially are small and are increased based on careful follow-up of secondary sexual characteristics and growth to achieve a relatively normal

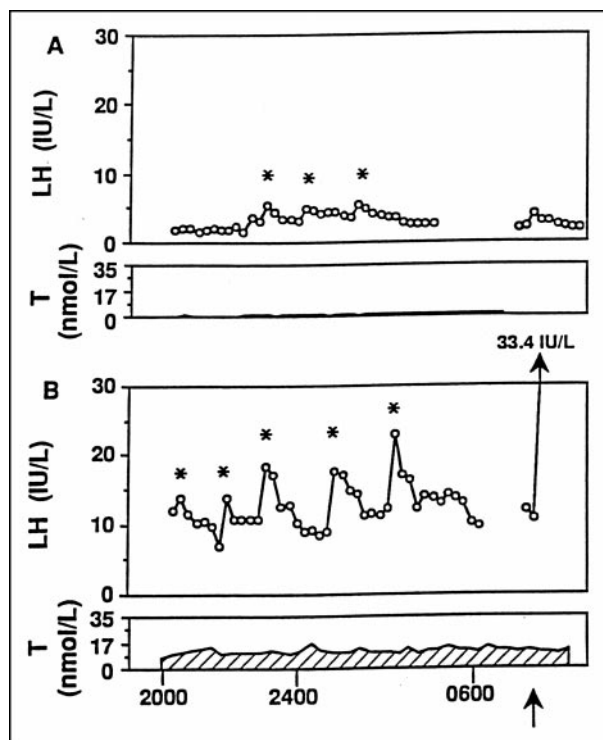


Figure 2. Results of frequent overnight gonadotropin and testosterone sampling at age 16.5 years (A) and 19 years, 4 months (B). Plasma luteinizing hormone (LH) values are shown in the top frames, and plasma testosterone values are shown in the lower frames. Gonadotropin-releasing hormone was administered at 0800 hours in the second study (arrow). Asterisks denote significant LH pulses. Reprinted with permission from Rosen DS, Kletter GB, Kelch RP. Puberty: what to do when the clock doesn't ring. *J Pediatr Endocrinol*. 1992;5:129.

puberty. Once puberty is complete, lifelong testosterone replacement is continued.

For girls who have hypogonadism, replacement hormone therapy is begun to coincide with puberty in peers. Estrogen replacement may be started with a transdermal estradiol patch or small daily doses of conjugated estrogens or ethinyl estradiol that are increased gradually to adult replacement levels. As with boys, careful monitoring of secondary sexual characteristics and growth is required. Cyclic hormonal replacement, typically with low-dose oral contraceptives, should be instituted after 1 to 2 years of estrogen replacement or once breakthrough bleeding has occurred.

Psychosocial Consequences of Delayed Puberty

Adolescents who have marked pubertal delay are at risk for psychosocial difficulties that should be sought ac-

tively in the initial evaluation. Delayed or absent puberty is more troublesome for boys than for girls. Significant delay may lead to poor body image, low self-esteem, teasing, bullying, parental overprotection, social withdrawal and isolation, declining academic performance, and school avoidance. Boys who look younger than their chronologic age have fewer opportunities for age-appropriate activities and social interaction, date less, and report feelings of unpopularity.

Girls who have pubertal delay present with fewer psychosocial concerns. Indeed, some value their immature body habitus. For girls who have eating disorders, for example, early puberty consistently is associated with increasing dissatisfaction with weight or body image.

The psychosocial burden imposed on the adolescent by delayed puberty should help to determine the extent of intervention. Simple reassurance may suffice when puberty is expected to proceed and psychosocial effects are few. Some form of hormonal therapy to accelerate puberty may be appropriate in cases of substantial psychosocial distress, even in cases of constitutional delay in which puberty is expected to progress spontaneously.

Suggested Reading

- Albanese A, Stanhope R. Investigation of delayed puberty. *Clin Endocrinol*. 1995;43:105-111
- Blyth DA, Simmins RG, Zakin DF. Satisfaction with body image for early adolescent females: the impact of pubertal timing within different school environments. *J Youth Adolesc*. 1985;14:207
- Brack CJ, Orr DP, Ingersoll G. Pubertal maturation and adolescent self-esteem. *J Adolesc Health Care*. 1988;9:280
- Brooks-Gunn J, Warren MP. The effects of delayed menarche in different contexts: dance and nondance students. *J Youth Adolesc*. 1985;14:285
- Ehrmann DA, Rosenfield RL, Cuttler L, Burstein S, Cara JF, Levitsky LL. A new test of combined pituitary-testicular function using the gonadotropin-releasing hormone agonist nafarelin in the differentiation of gonadotropin deficiency from delayed puberty: pilot studies. *J Clin Endocrinol Metab*. 1989;69:963
- Houchin LD, Rogol AD. Androgen replacement in children with constitutional delay of puberty: the case for aggressive therapy. *Baillieres Clin Endocrinol Metab*. 1998;12:427-440
- Kletter GB, Rolfes-Curl A, Goodpasture JC, et al. Gonadotropin-releasing hormone agonist analog (Nafarelin). A useful diagnostic agent for the distinction of constitutional growth delay from hypogonadotropic hypogonadism. *J Pediatr Endocrinol Metab*. 1996;9:9-19
- Lewis VG, Money J, Bobrow NA. Idiopathic pubertal delay beyond age fifteen: psychologic study of twelve boys. *Adolescence*. 1977; 12:1
- Rosen DS. Pubertal growth and sexual maturation for adolescents with chronic illness or disability. *Pediatrician*. 1991; 18:105
- Rosen D, Kletter GB, Kelch RP. Puberty: what to do when the clock doesn't ring. *J Pediatr Endocrinol*. 1992;5:129

PIR Quiz

Quiz also available online at www.pedsinreview.org.

6. The *most* common cause of delayed puberty in boys is:
 - A. Constitutional delay.
 - B. Hypothyroidism.
 - C. Kallman syndrome.
 - D. Klinefelter syndrome.
 - E. Mumps orchitis.
7. The *best* initial step in the etiologic assessment of delayed puberty is to obtain:
 - A. Bone age.
 - B. Karyotype.
 - C. Measurement of growth and sexual maturity.
 - D. Serum gonadotropin measurement.
 - E. Serum prolactin measurement.
8. A *true* statement about delayed puberty is that:
 - A. An etiologic laboratory investigation is usually positive for a treatable pathologic process.
 - B. Girls present more frequently than boys.
 - C. It is defined by a delay of more than 2 standard deviations from the mean age of pubertal onset.
 - D. It is defined by an absence of menarche by age 15 years.
 - E. Prevalence is 10% in otherwise healthy adolescents.
9. The *most* consistent presenting sign of bilateral gonadal failure in female adolescents is:
 - A. Congenital heart disease.
 - B. Growth retardation.
 - C. Learning disability.
 - D. Shield chest.
 - E. Web neck.
10. The *most* appropriate treatment in most adolescents who have constitutional delay is:
 - A. Caloric supplements.
 - B. Oral oxandrolone.
 - C. Reassurance.
 - D. Testosterone injections.
 - E. Thyroid replacement hormone.
11. A *true* statement regarding the psychosocial risks for pubertal delay is that:
 - A. Girls are affected more severely than boys.
 - B. Delayed maturation does not prevent males from dating and maintaining social relationships.
 - C. Hormonal therapy may be indicated in constitutional delay when the teen presents with significant psychological problems.
 - D. Pubertal delay rarely affects body image and self-esteem.
 - E. Boys are more likely to have associated eating disorders.