**Precocious Puberty**

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# Precocious Puberty

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Dr Muir did not disclose any financial relationships relevant to this article.

## Objectives

After completing this article, readers should be able to:

1. Know the normal ages of pubertal onset in boys and girls.
2. Discuss the clinical signs of puberty, their usual sequence of appearance, and their typical rate of progression.
3. Use the physiology of puberty to diagnose the cause of abnormal puberty.
4. Describe the factors involved in the appropriate management of precocious puberty.
5. Determine whether to follow or refer children who have signs of early puberty.

## Introduction

Although precocious puberty has standard clinical definitions and diagnostic tests are improving, the management of children who have signs of early puberty has become more complex in some ways during the last decade than ever before. This review illustrates how an understanding of the anatomy and physiology of puberty forms the foundation for managing children who experience puberty early.

## Case History

*A 4-year-old female has developed pubic hair in the past 3 months and has had an adult body odor for 6 months. She is otherwise healthy and has no pertinent findings on medical and surgical history. Her height and weight are just above the 97th percentile for age, and her physical examination reveals Sexual Maturity Rating (SMR) 2 breast and pubic hair development.*

## Definitions

By convention, normal puberty begins between ages 8 and 12 years in girls and between 9 and 14 years in boys. The lower ages of normal pubertal onset recently have been challenged, but a consensus to accept puberty among younger children as being normal without diagnostic evaluation has not been reached. Criteria for defining the five stages of puberty in boys and girls, proposed by Marshall and Tanner in 1969 and 1970, remain the standard (Fig. 1).

Thelarche (thē-lar'kē), the onset of female breast development, is characterized by tender nodules of firm tissue centered on the areolae, which usually are appreciable by palpation before they are by visual inspection. In overweight girls, palpation is essential to distinguish sex steroid-dependent breast (firm, nodular, and possibly tender) from adipose tissue (soft, homogeneous, and nontender). Adrenarche (ad'ren-ar'kē) is the onset of androgen-dependent signs of puberty (pubic hair, acne, and adult body odor). In females, adrenarche is the result of adrenocortical activity. In males, either adrenal or gonadal maturation can prompt adrenarche. Some sources refer to adrenarche as pubarche (pu-bar'kē). Menarche (mĕ-nar'kē) is the onset of menstruation.

## Epidemiology

The estimated incidence of precocious puberty in the United States is 0.01% to 0.05% per year. It is 4 to10 times more frequent in females than in males and more common among African-American than among Caucasian children. A century-long secular trend reduced the age of menarche by about 0.3 years per decade until the 1960s. At that point, the rate of decline in developed countries slowed or even stopped. In the United States, the mean

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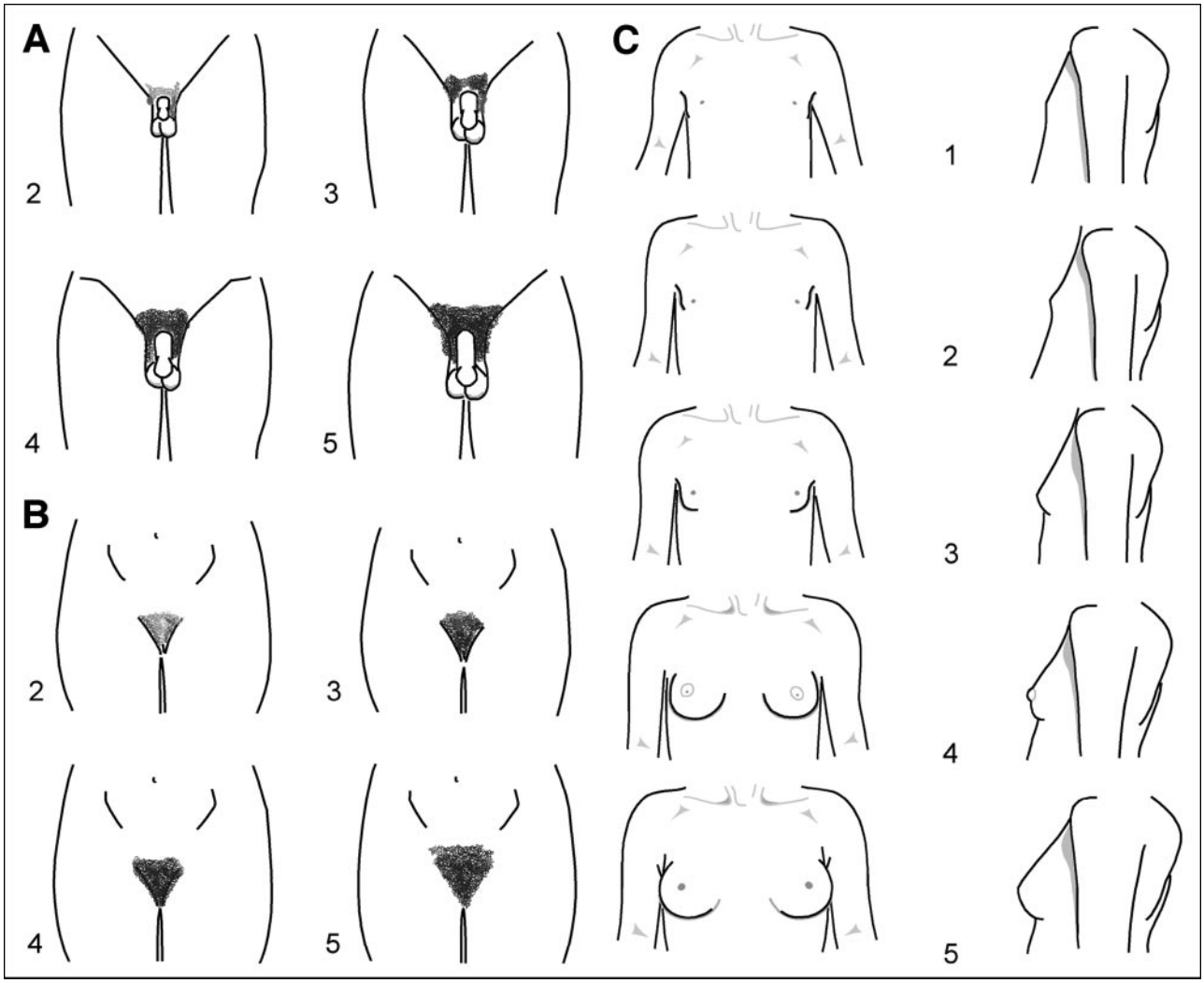


**Figure 1.** Stages of normal puberty described by Marshall and Tanner. A. The normal progression of male puberty. Sexual Maturity Rating (SMR) 1 (not shown) is prepubertal, with testicular volumes less than 4 mL, a thick and rugated scrotum, and an immature penis. By SMR 2, coarse, sex steroid–dependent hair has appeared on the pubis, but it is sparse and does not typically meet in the midline. The penis remains immature, but scrotal thinning and testicular enlargement have begun. SMR 3 is characterized by pubic hair meeting at the midline and the start of penis growth, predominantly in length. At SMR 4, the pubic hair growth is dense and continuous, but has not reached a full adult pattern. The penis has enlarged in both length and circumference. SMR 5 is that of full adult development. B. Normal pubic hair development of the female. The descriptions are similar to those for male pubic hair growth. C. Normal progression of breast development. Stage 1 is the normal prepubertal state. Tender "buds" are felt and seen at stage 2, and stage 3 is characterized by further development of breast tissue well beyond the areolar diameter and incomplete nipple development. Stage 4 is easily recognized by secondary elevation of the areola above the contour of the breast, and by stage 5, this areoloar elevation recedes to the plane of the surrounding breast.

age of menarche in Caucasians is near 12.7 years and in African-Americans is about 12.2 years (Table 1). The age of adrenarche in females is also race-dependent. The mean age of adrenarche in African-American girls is approximately 8.8 years compared with about 10.5 years in Caucasian girls. In a 1997 report, the ages of thelarche among some 17,000 healthy American children were 10.0 and 8.9 years for Caucasians and African-Americans, respectively. These ages were about 6 to 12 months lower than those reported a decade earlier. More surprisingly, a significant number of girls had thelarche during or before their seventh year. Some of these cases

**Table 1. Pubertal Milestones**

| | Mean Age of Pubertal Milestone (y) | | | |
|---|---|---|---|---|
| | Adrenarche | Menarche | Start of Growth Spurt | Testicular Volume >3 mL |
| Female | | | | |
| African-American | 8.8 | 12.2 | — | — |
| Caucasian | 10.5 | 12.7 | 9.8 | — |
| Male | 12.0 | — | 11.5 | 11.5 |

of early thelarche may reflect inaccurate reporting because assessments were made by observation rather than by palpation. Nonetheless, the age of thelarche in American children appears to be declining, whereas the age of menarche is remaining stable. Typically, menarche occurs about 2 years after thelarche, with longer intervals in girls who have early breast development and shorter intervals in girls whose breast development is later.

Male puberty is more difficult to assess in research settings than is female puberty. Using increased testicular size to mark pubertal onset, most studies report a mean age of pubertal onset near 11.5 years in males (Table 1). Adrenarche typically is seen around the 12th birthday in boys, with African-Americans having a slightly lower mean age of onset compared with Caucasians. Males take an average of 4 years to progress through puberty.

Genetic and environmental factors influence the onset of puberty. Improved nutrition is considered the primary reason for the secular decline in pubertal age. Furthermore, childhood obesity has been associated in longitudinal studies with early puberty in girls. However, there are other important determinants of puberty. Precocious puberty was noted among children who had been adopted recently from a developing to a developed county. This was seen more frequently among girls than boys and could not be explained entirely by changes in nutrition, body weight, or body fat. Birth date uncertainty accounts for a portion of the children believed to have early pubertal development. Other environmental determinants, however, may include stress, climate and light cycles, and chemical exposures.

Environmental determinants of puberty are important because such exposures can be changed when necessary. It appears likely, however, that among healthy children in developed countries, genetic influences on puberty outweigh the environmental influences by a factor of about three. Genetic determinants of pubertal onset were demonstrated in traditional twin studies in which the correlation coefficient between age of pubertal onset in monozygotic twins exceeded that in dizygotic twins. As expected, the correlation in dizygotic twins was equal to that seen in singleton siblings. Currently, candidate puberty control genes include steroid hormone receptors, biosynthetic and catabolic enzymes, and transcription factors.

## Pathogenesis

Much as neurologists are challenged to locate the anatomic site of a lesion, clinicians assessing children who have precocious puberty must identify the source of pubertal signals (Fig. 2 and Table 2). Lesions may involve neural signals, hormones, receptors, and postreceptor signals. Abnormal levels of sex steroids can be derived from endogenous (adrenal or gonadal) or exogenous sources. If the source is gonadal, the dependence of sex steroid production on gonadotropin activity must be determined. Gonadotropin-dependent puberty arises from either central dysregulation, causing overproduction of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), or ectopic hormone production, usually a neoplasm producing human chorionic gonadotropin (hCG).

## Control of Normal Pubertal Onset

Because central dysregulation is the most frequent cause of precocious puberty, it is useful to review the physiology of puberty. Hypothalamic neurons produce gonadotropin-releasing hormone (GnRH), a decapeptide that travels through a portal venous system to the anterior pituitary gland, where it induces pulsatile release

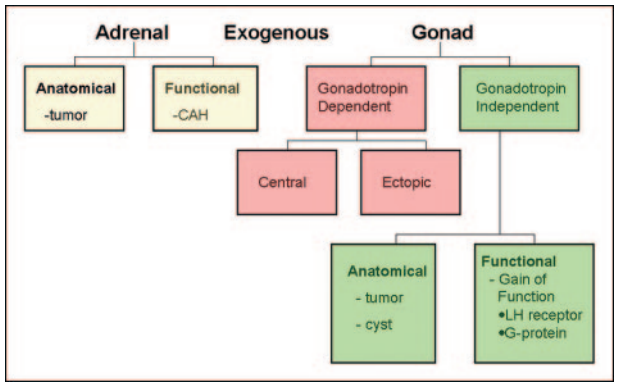


**Figure 2.** Causes of precocious puberty. This approach to identifying a cause of precocious puberty works by determining the source of the sex steroids that are inducing pubertal features. CAH=congenital adrenal hyperplasia, LH=luteinizing hormone

**Table 2. Differential Diagnosis of Precocious Puberty**

| Category | Diagnosis |
|---|---|
| Central (Gonadotropin-dependent) | Idiopathic—most frequent cause<br>Adoption from underdeveloped to developed region<br>Tumor—eg, astrocytoma, glioma, germinoma<br>Congenital anomaly—eg, hydrocephalus, hamartoma<br>Infection/postinfection—encephalitis, meningitis<br>Radiation—usually >18 cGy<br>Trauma—neurosurgical, nonsurgical<br>Ischemia |
| Gonadal Steroid-dependent (Gonadotropin-independent) | McCune-Albright syndrome—females predominate<br>Familial male-limited precocious puberty<br>Gonadal neoplasia (benign, malignant)<br>Ovarian follicular cyst<br>Leydig cell nodular hyperplasia<br>Aromatase excess<br>Human chorionic gonadotropin-secreting tumor<br>Primary hypothyroidism<br>Exogenous steroids (oral contraceptive pills, skin creams, testosterone) |
| Adrenal Steroid-dependent (Gonadotropin-independent) | Congenital adrenal hyperplasia<br>—21 hydroxylase deficiency<br>—11 hydroxylase deficiency<br>11 hydroxysteroid dehydrogenase deficiency<br>Glucocorticoid resistance<br>Adrenal tumor (benign, malignant)<br>Adrenal rest tumors<br>Exogenous steroids (eg, dehydroepiandrosterone) |
| Incomplete Precocious Puberty (Gonadotropin-independent) | Premature thelarche<br>Premature adrenarche<br>Premature menarche—look for gynecologic cause |

of two gonadotropins: LH and FSH. These related heterodimeric glycoproteins share a common alpha chain, but have unique beta chains. After transport to the gonads, gonadotropins bind membrane receptors that are coupled to G-protein complexes within target cells. In females, LH enhances thecal cell production of androgens and granulosa cell production of progesterone. FSH stimulates granulosa cell production of estrogen. In males, LH stimulation of Leydig cells causes testosterone production, and FSH stimulation of Sertoli cells is vital for germ cell development.

The hypothalamic-pituitary-gonadal axis is functional by 20 weeks' gestation and remains active throughout much of the remaining gestation. A brief spurt of central pubertal axis activity on the first day after birth is followed by a period of quiescence. During the first postnatal month, GnRH pulses recur spontaneously. In males, this infantile central activity reduces to near prepubertal levels by about 3 to 6 months of age. Gonadotropin secretion, particularly of FSH, may persist in females until 18 months of age. During the subsequent prepubertal period, gonadotropin secretion is minimal and cannot be stimulated by a single intravenous GnRH infusion. As puberty begins, gonadotropins are released from the pituitary gland in a pulsatile fashion, particularly at night. With increased gonadotropin release comes the ability of exogenous GnRH to stimulate release of FSH and later both LH and FSH.

Normal onset of puberty is determined by multiple incompletely understood intracerebral processes. In a simplified model, gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter that inhibits GnRH secretion. In contrast, glutamatergic neurotransmission stimulates GnRH production. Changes in the balance of these signals trigger puberty. It is not yet known whether GABA-mediated neurotransmission is reduced at pubertal onset, allowing increased glutamatergic signals, or vice versa. The results of recent investigations of the ligand-receptor pair of Kisspeptin-1 and GPR54 need to be incorporated into the neurochemical model of puberty. Kisspeptin-1, released by forebrain neurons, becomes an efficient activator of GPR54 on GnRH-secreting neurons at the time of puberty, and this activation is associated with GnRH release. Much, however, remains to be learned. For example, GnRH production is influenced by neuropeptides, such as neuropeptide Y and norepinephrine. Furthermore, neurocommunications exist between astroglial cells and GnRH-producing neurons.

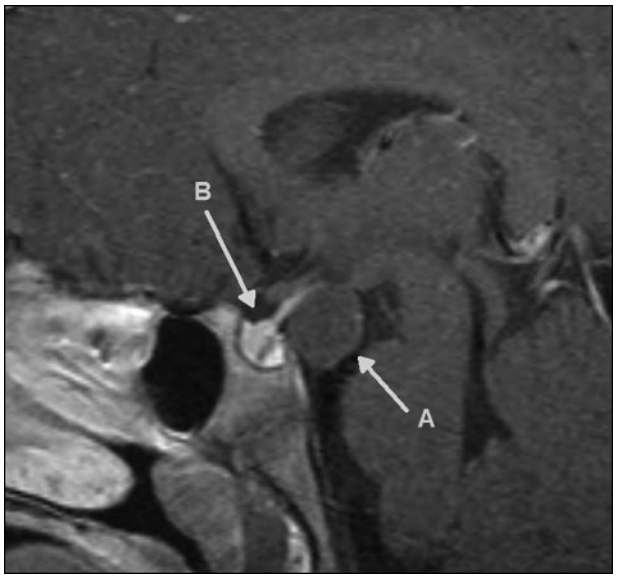


**Figure 3.** Hamartoma of the tuber cinereum. Median section shows the large mass (A) lying posterior to the pituitary gland (B).

## Applying Physiology to Precocious Puberty

Currently, no cause for central precocious puberty can be found in two thirds or more of affected girls. An identifiable cause is much more likely to be found in males. As detailed in Table 2, disturbances of the hypothalamus or higher neurologic centers can result in abnormal GnRH release. Hypothalamic hamartomas are nonneoplastic, congenital malformations that contain GnRH-secreting cells. The masses have a typical radiographic appearance and are nonprogressive (Fig. 3). Autonomous production of gonadotropins by a pituitary adenoma is a very rare cause of premature puberty. Gonad stimulation by hCG produced in tumors (usually in brain, liver, mediastinum) can appear clinically similar to true central disease, but is not associated with elevations of LH and FSH. Cross-reactive binding of hCG, however, occurs in some commercial LH assays.

Gonadotropin-independent sexual precocity can arise from a variety of anatomic or functional lesions that are discussed only briefly here. Benign or malignant tumors of the adrenal cortex or gonad can produce sex steroids autonomously. Follicular ovarian cysts may cause transient or persistent signs of puberty. Usually, estrogen-dependent effects, such as breast development, maturation of the vaginal mucosal, or vaginal bleeding, predominate.

Biosynthetic defects of glucocorticoids causing congenital adrenal hyperplasia (CAH) and glucocorticoid resistance are conditions that raise ACTH-induced production of adrenocortical androgens (Fig. 4) and cause premature adrenarche and rapid skeletal growth in males and females. Clitoromegaly can occur in girls, but normal phallus size is seen in males. Central precocious puberty also can arise in children who have CAH if their bone age advances to the age of normal pubertal onset.

Prolonged hypothyroidism is a curious cause of precocious puberty that may result from gonadotropin-like action of thyroid-stimulating hormone (TSH) or activation of gonadotropin receptors by TSH. TSH is another heterodimeric glycoprotein that shares the alpha chain of gonadotropins. Hyperprolactinemia, induced in hypothyroidism by high concentrations of thyrotropin-releasing hormone, may sensitize the ovary to gonadotropins.

A number of genetic lesions in hormone synthetic enzymes, receptors, and postreceptor signals cause abnormal sex steroid production. Excess aromatase activity, converting androgens to estrogens, has been reported to cause premature thelarche in girls and gynecomastia in boys. Mutations of the LH receptor can result in unbridled Leydig cell activity and the syndrome of familial male-limited precocious puberty (testotoxicosis). Constitutive postreceptor signals from mutated stimulatory G-protein complexes cause the McCune-Albright syndrome (precocious puberty, café au lait macules, polyostotic fibrous dysplasia).

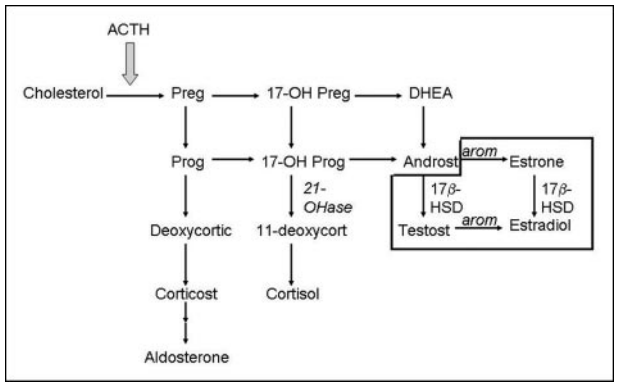


**Figure 4.** Simplified scheme of adrenal and gonadal steroid production. Specific enzyme actions are highlighted. In the rate-limiting step of steroid biosynthesis, ACTH drives the production of pregnenolone in response to lowering concentrations of cortisol. Deficiency of 21-hydroxylase (21-OHase) causes congenital adrenal hyperplasia and is diagnosed by the presence of high serum concentrations of 17-hydroxyprogesterone. Gonadal sex steroid production (boxed) is distinguished from adrenal sex steroid production by the activity of 17 beta-hydroxysteroid dehydrogenase (17 beta-HSD). Aromatase (arom) is more active in ovaries than in testes. It also is active in adipose tissue, often contributing to gynecomastia in adolescent males.

Sources of exogenous sex steroids can include oral contraceptives, skin creams, meat from hormone-treated animals, plant phytoestrogens, and anabolic steroids. Unless a hormone preparation contains both androgens and estrogens, exogenous steroid exposure usually causes a picture of incomplete puberty.

Other syndromes of incomplete puberty include benign premature thelarche and adrenarche. In the former condition, unilateral or bilateral breast development is observed with minimal or no other clinically apparent estrogen effects. About 60% of cases are identified between 6 to 24 months of age, and diagnosis after 4 years is unusual. Normal, rather than accelerated, growth velocity and minimal progression of breast development distinguish this condition from those that require treatment. Importantly, about 10% of girls who have typical benign idiopathic thelarche eventually develop true central precocious puberty and require treatment. Children who have premature adrenarche have isolated signs of adrenal sex steroid production (pubic hair, acne, body odor) that progress slowly and are associated with normal growth velocity and a height commensurate with their skeletal maturation (bone age). Children who experience intrauterine growth restriction are at risk for this condition. Although treatment of idiopathic premature adrenarche is not recommended in children, some 20% of affected girls develop clinically significant ovarian hyperandrogenism as adults.

**About 60% of cases of premature thelarche are identified between 6 and 24 months of age. . . .**

## Clinical Evaluation

### History

The medical history should define which features of puberty are present, their duration, and the rate of progression. Questioning should seek abnormalities of other anterior and posterior pituitary gland function, neurologic (especially visual) dysfunction, or intracranial mass effects. Pelvic pain may indicate ovarian pathology, and symptoms of systemic illness may indicate the presence of a tumor. Virilizing adrenocortical tumors may be accompanied by Cushing syndrome. A family history of premature puberty may suggest the presence of a genetic condition.

### Physical Examination

The linear growth spurt is a feature of early puberty in females. Maturation of the vaginal mucosa is a sensitive indicator of estrogen activity that may appear before breast tissue can be appreciated. Clitoromegaly, a sign of abnormally high androgen levels, is never part of normal female puberty. The first signs of male puberty are thinning of the scrotum and enlargement of the testes beyond 3 mL. The Prader orchidometer is used to determine testicular volume, although testicle length standards also are available. Growth of the phallus and pubic hair follow. The skeletal growth spurt usually peaks at SMR 4 in males. Dental development provides the examiner a simple method of approximating bone age in both females and males.

Much can be learned from the testicular examinaton of boys who have early puberty. Testicle volumes greater than 3 mL bilaterally usually indicate gonadotropin action. Lesions causing premature testicular enlargement, however, are not always neurologic. Owing to the selective stimulation of Leydig cells by hCG, testes that have been exposed to tumor-derived hCG exceed the size of prepubertal gonads, but are smaller than those seen in children who have true central precocity. Familial male-limited precocious puberty causes bilateral testicular enlargement and usually is suspected because of the young age of onset and a family history of sexual precocity in males. Testicular tumors typically are unilateral, although bilateral adrenal rest in boys who have poorly controlled CAH is a cause of bilateral testicular enlargement. Testes of prepubertal size in a boy who has isosexual precocious puberty usually indicates that androgen is arising from either the adrenal gland or an exogenous source.

### Laboratory Evaluation

The diagnostic laboratory evaluation of children who experience early puberty should confirm the source of hormone. The normal ranges of pubertal hormones vary with the stage of pubertal development. When interpreting hormone results, it is important, therefore, to determine whether a result is consistent with the stage of pubertal development, rather than with the child's chronologic age. For a child whose hepatic function is normal, the serum dehydroepiandrosterone sulfate (DHEA-S) concentration provides an estimate of adrenocortical sex steroid production. Values elevated beyond that expected for pubertal stage suggest adrenal pathology (eg, CAH, adrenal tumor). Biosynthetic defects of adrenocortical steroids are

identified best by high concentrations of the substrate for the enzyme that is deficient. For example, 21-hydroxylase deficiency is diagnosed by determining the serum 17-hydroxyprogesterone concentration (Fig. 4). Random measures of testosterone or estradiol are helpful for detecting gonadal steroid production. Advanced bone age, especially if it has progressed beyond the height age, serves as a nonspecific biomarker of abnormal sex steroid production. Among children who have idiopathic central precocious puberty, bone age helps determine whether treatment to stop additional development will be of value.

Because normal pituitary gland secretion of gonadotropins is pulsatile, randomly obtained serum samples do not reliably contain enough LH and FSH to permit traditional assays to diagnose the onset of puberty. Although today's most sensitive gonadotropin assays may be able to distinguish between basal gonadotropin levels of prepubertal and pubertal children, most commercial gonadotropin assays do not. Therefore, definitive demonstration of an activated central axis driving early puberty usually requires stimulation testing with exogenous GnRH. A single injection of GnRH will not increase the serum gonadotropin concentrations in children who have a quiescent central pubertal axis (ie, prepubertal or precocious puberty from noncentral dysfunction). Once the hypothalamic-pituitary axis has become active, however, the injection causes a rise of FSH in early puberty, and increased LH release is the most specific indicator of central puberty. The demonstration of central precocious puberty by GnRH testing should prompt a magnetic resonance study of the brain with high-resolution imaging of the hypothalamus and pituitary gland.

**The demonstration of central precocious puberty should prompt a magnetic resonance study of the brain. . . .**

## Management

Although general pediatricians may follow children who have premature adrenarche or thelarche, initial evaluation and management of precocious puberty often requires subspecialty consultation. When a primary cause of precocious puberty can be identified, treatment of that condition is paramount. Judgment is required to determine whether central precocious puberty requires intervention. Whereas some intracerebral tumors that cause early puberty may require surgery for complete resection or preservation of normal cerebral function, other tumors (eg, germinoma) may be radiosensitive. A nonprogressive central lesion, such as a hamartoma, usually is treated medically. Many children who have central precocious puberty require treatment solely to delay additional maturation. Clinical features suggesting that medical intervention to arrest central precocious puberty will benefit the patient are male sex, age younger than 6 years, skeletal age advancing more rapidly than height age, and psychosocial disturbances (eg, menses will be arrested). GnRH agonist (eg, leuprolide) therapy is the most effective medical therapy available for central precocious puberty. Tonic stimulation of the pituitary gland results in a short period of pubertal stimulation, followed by down-regulation of GnRH receptors and reduced gonadotropin synthesis. Although antagonists to GnRH (eg, cetrorelix, ganirelix) are not yet approved for use in precocious puberty, they promise to suppress puberty without the initial gonadotropin stimulation seen with current agents.

The management of autonomous gonadal steroid secretion in McCune-Albright syndrome and familial male-limited precocious puberty can be difficult. Medications to block: a) steroid production (eg, ketoconazole), b) 5-alpha reductase activity (eg, finasteride), c) steroid receptors (eg, flutamide, spironolactone), and d) aromatase activity (eg, testolactone, anastrozole) have been suggested, but formal trials are limited.

Children who have severe brain dysfunction and central precocious puberty present special ethical concerns. GnRH therapy may reduce behavioral problems and provide effective contraception. Therefore, it may be tempting to offer this treatment to children who have limited cognitive abilities and multiple special care needs. Reduced bone mineral density, eunuchoid growth, and ethical considerations arising from "chemical castration," however, are important disadvantages that must be considered.

Adrenocortical steroid production of androgens can be controlled with glucocorticoid replacement in patients who have CAH. This treatment, however, may be ill advised for children who have late-onset forms of

21-hydroxylase deficiency and who are able to mount a normal glucocorticoid response to stress and predicted to have a normal final height. The risk of iatrogenic adrenocortical suppression may outweigh any benefits that treated children may accrue from chronic glucocorticoid therapy.

## Prognosis

The cause of precocious puberty determines the prognosis. In most cases, central precocious puberty is arrested by adequate treatment with GnRH agonists. Menses stop, although a single period may occur 2 weeks after therapy has been started. Breast, pubic hair, testicular, and phallus growth stop and often regress. Skeletal growth and maturation slow to age-appropriate rates. Serum testosterone or estradiol concentrations fall to prepubertal levels, and GnRH infusions induce insignificant changes in serum LH or FSH concentrations. Apart from the immediate benefits of GnRH agonist therapy, final height in children who have central precocious puberty may increase by 8 to 12 cm compared with the heights of children diagnosed as having the same condition before therapy was available. Earlier treatment is associated with improved final height. The combined use of growth hormone and GnRH agonists is controversial, but may allow more growth in children who are particularly short. Once treatment has been stopped, puberty usually resumes and progresses at a normal rate.

## Summary

General pediatricians must be able to distinguish children who are growing normally from those who are not. An understanding of the regulation and effects of sex steroid production allows clinicians to determine whether a child who has precocious puberty requires observation or should be referred to a subspecialist for evaluation and treatment.

## Suggested Reading

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## PIR Quiz

Quiz also available online at www.pedsinreview.org.

6. An 8-year-old African-American girl has recently developed pubic hair and adult body odor. She also has scattered comedones and papules on her cheeks and forehead. On examination, her sexual maturity rating (SMR) for pubic hair is 3. SMR for breast tissue is 1. Her linear growth velocity continues along the percentile established by age 2 years. The *most* appropriate conclusion is that she:

   A. Has been exposed to a large dose of exogenous estrogen.
   B. Is experiencing normal adrenarche.
   C. Requires immediate evaluation for a masculinizing tumor.
   D. Will have elevated concentrations of thyroid-stimulating hormone (TSH).
   E. Will have pubertal concentrations of follicle-stimulating hormone (FSH).

7. A 2-year-old Caucasian girl has had stable SMR stage 3 breast development for the past 9 months. Her linear growth velocity has remained at the 75th percentile since age 1 year. The remainder of her examination findings are normal. The *most* appropriate conclusion is that she:

   A. Has a reduced risk for developing central precocious puberty compared with other girls of the same age who have no breast development.
   B. Has been exposed to a large dose of exogenous estrogen.
   C. Is experiencing benign premature thelarche.
   D. Must be evaluated for precocious puberty now.
   E. Needs suppressive doses of gonadotropin-releasing hormone (GnRH) to prevent short stature.

8. An 8-year-old boy has recently experienced accelerated statural growth, impressive muscular development, and enlargement of his phallus. His testicles are symmetric, each having a volume of 3 mL. The *most* appropriate conclusion is that he:

   A. Is undergoing normal puberty.
   B. Likely has a human chorionic gonadotropin-producing tumor.
   C. Likely has a very elevated concentration of dehydroepiandrosterone sulfate (DHEA-S).
   D. Will have pubertal concentrations of serum leutinizing hormone (LH).
   E. Will show an impressive increase in FSH in response to an injection of GnRH.

9. An 8-year-old boy has recently experienced accelerated statural growth, impressive muscular development, and enlargement of his phallus. His testicles are symmetric, and each has a volume of 8 mL. An injection of GnRH results in increased LH release. The *most* appropriate next step is:

   A. Bone age studies of the wrist.
   B. Magnetic resonance imaging of the brain and pituitary gland.
   C. Serum DHEA-S measurement.
   D. Serum 17-hydroxyprogesterone measurement.
   E. Serum testosterone measurement.

10. An 8-year-old boy of normal intelligence has been diagnosed with idiopathic central precocious puberty. Time-limited treatment with the GnRH agonist leuprolide *most* likely will:

   A. Increase adult stature compared with no treatment.
   B. Increase the risk of osteoporosis.
   C. Produce irreversible gynecomastia.
   D. Produce permanent chemical castration.
   E. Selectively diminish expected adult phallus size.

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