

Precocious Puberty

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OBJECTIVES

After completing this article, readers should be able to:

1. Define precocious puberty in girls according to race.
2. Identify the specific cause of central precocious puberty (CPP) or pseudoisosexual precocious puberty.
3. Define how the administration of the agonist of gonadotropin-releasing hormone (GnRH_a) affects the hypothalamic-pituitary-gonadal axis, sex hormone secretion, and sexual development.
4. Describe the child for whom treatment with GnRH_a should be reserved.
5. Identify which children who have apparent premature thelarche and evolve into ones who have CPP can be treated effectively with GnRH_a.

Introduction

Isosexual precocious puberty is the appearance of physical signs of sexual development in keeping with the phenotypic gender of the child prior to the earliest accepted age of sexual maturation. Precocious puberty is of concern because of the underlying disorders that may cause premature sexual development, the short adult stature that may result from rapid skeletal maturation attributable to early secretion of sex hormone, and the psychosocial difficulties that the sexually precocious child may encounter.

Normal Puberty

PHYSICAL DEVELOPMENT

The Sexual Maturity Rating (SMR) (Tanner) stages of sexual development are described in Tables 1 and 2. In girls, breast budding (thelarche) is usually the first sign of puberty; pubic hair growth (pubarche) is the initial pubertal sign in 15% of girls. Menarche occurs an average of 2 years after thelarche (range, 1 to 5 y), and peak height velocity (PHV) is reached at 12 years in girls immediately prior to menarche. Pelvic ultrasonography demonstrates a progressive increase in uterine length and ovarian volume during sexual maturation, correlating with breast growth and serum estradiol

concentrations, although these stages overlap substantially. In addition to an increase in volume, the ovarian echogenic pattern varies with advancing puberty as multiple, initially small and then somewhat larger, follicular cysts appear and regress; in the late adolescent female, a multicystic ovarian sonographic pattern is common.

In boys, the earliest physical sign of puberty is testicular enlargement (long diameter >2.5 cm, volume >4 mL). Pubertal development progresses at a relatively slow pace through SMR stage III male genital development and then accelerates; approximately 4 years elapse between genital stages II and V. PHV is achieved at the average age of 14 years.

There is substantial variation in the onset and duration of puberty for both genders. Those in whom the timing and progression of sexual maturation are "shifted to the left" experience early puberty, at times a familial characteristic. When sexual development begins before the youngest accepted age, that child has precocious puberty.

In girls, the age before which pubertal onset has been considered precocious long has been 8 years. However, new data indicate that breast development before 6 to 7 years in Caucasian girls and before 5 to 6 years in African-American girls is a more appropriate criterion. Thus, it recently has been reported that at 3 years of age, 3%

of African-American and 1% of Caucasian girls have either thelarche or pubarche, with the percentages increasing to 5.7% and 1.9% at 5 years and to 27.2% and 6.7% at 7 years, respectively (Fig. 1). At each age, the sexual maturation of African-American females is more advanced than that of Caucasian females. Menarche occurs in 2.3% of African-American females by 7 years of age compared with 0.2% of Caucasian females; by 11 years the percentages are 27.9% and 13.4%, respectively. However, mean menarcheal age has not changed (African-American, 12.2 y; Caucasian, 12.9 y). On the other hand, African-American and Caucasian males appear to mature at comparable ages. Sexual development before 9 years of age is considered precocious in boys of either ethnic background.

HORMONES

Skeletal maturation (bone age) and increase in bone mineralization parallel the progression of chronologic age under the influence of growth and thyroid hormones, estrogens, and androgens. Estrogen is responsible for epiphyseal fusion and attainment of adult bone mineral density. As measured by magnetic resonance imaging, the height of the anterior

ABBREVIATIONS

CNS:	central nervous system
CPP:	central precocious puberty
DHEA:	dehydroepiandrosterone
DHEAS:	dehydroepiandrosterone sulfate
FSH:	follicle-stimulating hormone
GH:	growth hormone
GnRH:	gonadotropin-releasing hormone
GnRH _a :	agonist of gonadotropin-releasing hormone
hCG:	human chorionic gonadotropin
HPG:	hypothalamic-pituitary-gonadal
LH:	luteinizing hormone
PHV:	peak height velocity
SMR:	Sexual Maturity Rating

*Editorial Board.

TABLE 1. SMR (Tanner) Breast and Pubic Hair Stages and Ages of Sexual Development in Females

STAGE	AGE (Y)		UTERINE LENGTH (CM)	OVARIAN VOLUME (ML)
	W	AA		
Breast				
I.	None			3.3 (2.2–4.9) 1.5 (0.9–2.1)
II.	Breast bud diameter ≤ areola width	9.96±1.82	8.87±1.93	3.5 (2.3–5.2) 2.1 (1.1–3.2)
III.	Breast diameter > areolar width Peak height velocity Menarche	11.30±1.42 12.2 (10.2–14.2) 12.88±1.20	10.19±1.42 12.16±1.21	5.8 (5.3–6.9) 2.4 (1.2–4.0)
IV.	Mounding of areola above plane of breast	12.9 (10.4–15.3)		5.5 (3.5–7.1) 3.0 (1.9–4.9)
V.	Adult	14.5 (11.3–17.8)		6.9 (5.9–7.7) 3.2 (2.5–5.6)
Pubic Hair				
I.	None			
II.	Slightly pigmented over mons or labia	10.51±1.67	8.78±2.00	
III.	Dark, coarse on mons	11.53±1.42	10.35±1.42	
IV.	Adult in character, confined to mons	12.6 (10.4–14.8)		
V.	Adult—spread to medial thigh	14.6 (12.4–16.8)		
<p><i>Data from Herman-Giddens PA, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings Network. Pediatrics. 1997;99:505–512 and Orbak Z, Sagsoz N, Alp H, Tan H, Yildirim H, Kaya D. Pelvic ultrasound measurements in normal girls: relation to puberty and sex hormone concentrations. J Pediatr Endocrinol Metab. 1998;11:525–530.</i></p> <p><i>W=White; AA=African-American; ovary volume calculated as an ellipse (length × width × depth × 0.5233); ±=1 standard deviation; (range)</i></p>				

pituitary lobe increases during sexual maturation to a maximum of 7 mm as its superior border changes from concave to convex. After intense activity of the hypothalamic-pituitary-gonadal (HPG) axis in the mid-fetal, neonatal, and early infancy periods, there is an interlude between 2 and 8 years of age during which the HPG is relatively quiescent due to the inhibitory influences exerted by higher central nervous system (CNS) centers. Even during this interval, however, there is pulsatile release of low amounts of hypothalamic gonadotropin-releasing hormone (GnRH), measurably increased nocturnal secretion of luteinizing hormone (LH), and GnRH-stimulated secretion of LH and follicle-stimulating hormone (FSH) in both genders.

The onset of puberty is characterized hormonally by an increase in the frequency and amplitude of the GnRH “pulse generator” that is reflected by a rise in basal serum

LH and FSH concentrations, augmentation of nocturnal LH secretion, and an increase in the LH secretory response to exogenous GnRH. In females, the FSH secretory response to GnRH declines with advancing pubertal development, and the GnRH-stimulated peak LH/FSH ratio increases (Tables 3 and 4). Gonadarche is manifested by increased secretion of estradiol in girls and testosterone in boys. In females, the cyclic pattern of HPG function develops as the processes of ovarian oogenesis and ovulation mature. There is also a peripubertal increase in the secretion of the adrenal androgens dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), with adrenarche usually beginning between 6 and 8 years in both genders. Adrenarche and gonadarche may be dissociated in several disorders of puberty, including primary hypogonadism (Turner syndrome) and isosexual precocity. During puberty there is a marked

increase in the spontaneous secretion of growth hormone (GH) as well as in the GH secretory response to provocative stimuli and in serum concentrations of insulin-like growth factor-I.

Causes of Isosexual Precocious Puberty

Isosexual precocious puberty is several-fold more common among girls than boys. Approximately 50% of children who have isosexual precocity have true and complete central precocious puberty (CPP) (Table 5). In CPP, pubertal development is driven by GnRH, as the “restraint” placed on the HPG axis by higher CNS centers is removed, which is the same mechanism that brings about normal sexual development. CPP may be due to congenital anomalies; infectious, neoplastic, or traumatic insults to the CNS; or treatment of long-standing sex hormone exposure due to pseudoiso-

TABLE 2. SMR (Tanner) Genital and Pubic Hair Stages and Ages of Sexual Development in Males

STAGE		AGE (Y)
Genitalia		
I.	Prepubertal testis <2 cm	
II.	Testis >2.5 cm, >4 mL	11.8 (9.8–14.2)
III.	Testis >3 cm, >6 mL; phallus has grown in length Peak height velocity	13.0 (11.7–14.6) 13.8 (11.5–16.0)
IV.	Testis >4 cm, >10 mL; phallus has grown in breadth	14.3 (12.6–15.8)
V.	Adult testis >5 cm, >15 mL	15.1 (12.9–17.0)
Pubic Hair		
I.	None	
II.	Slightly pigmented at base of phallus or on scrotum	12.2 (10.7–13.8)
III.	Dark, coarse at base of phallus	13.9 (12.0–15.7)
IV.	Adult in character; confined to suprapubic region	14.8 (12.9–16.4)
V.	Adult—spread to medial thigh	15.3 (13.8–16.8)

Data from Lee PA. Disorders of puberty. In: Lifshitz F, ed. *Pediatric Endocrinology*. 3rd ed. New York, NY: Marcel Dekker Inc; 1996: 175–195.

sexual precocity. In females, CPP most often is idiopathic (95%), although frequently an asymptomatic hypothalamic hamartoma with GnRH-synthesizing neurons may be identified by CNS imaging. A CNS insult or structural abnormality may be found in more than 90% of boys who have CPP. Both septo-optic dysplasia and cranial radiation therapy lead to deficiencies of multiple anterior pituitary hormones, including GH; however, paradoxically, in many of these children the HPG axis remains intact and begins to function at a prematurely young age.

Hypothalamic, pineal, and mediastinal germinomas secrete human chorionic gonadotropin (hCG), thereby stimulating Leydig cell secretion of testosterone in boys independently of GnRH and LH, examples of pseudoisosexual precocious puberty. Familial male-limited precocious puberty (testotoxicosis) is due to a germ-line mutation in the LH receptor that renders it constitutively active; that is, it behaves as if it were being stimulated by its natural ligand (LH) and, thus, “turns on” Leydig cell testosterone synthesis. The McCune-Albright syndrome is due to a germ-line mutation that leads to a constitutively active G α_s subunit of the guanosine triphosphate binding protein, the membrane-bound signaling molecule linked to the LH receptor, and results in both Leydig cell synthesis of testosterone and granulosa cell production of estradiol. Ovarian cysts, granulosa, and Leydig cell gonadal tumors also secrete sex hormones independently of gonadotropin control and are, at times, due to somatic tissue-specific mutations in the LH receptor or the G α_s subunit of the G-protein.

Congenital adrenal hyperplasia due to deficiency of either 21- or 11 beta-hydroxylase leads to excessive secretion of testosterone and pseudoisosexual precocious puberty in males. In some girls who have primary hypothyroidism, thelarche and uterine bleeding occur; in males, macro-orchidism may result, although excessive phallic and pubic hair growth seldom are seen. In this complex, precocious puberty may be

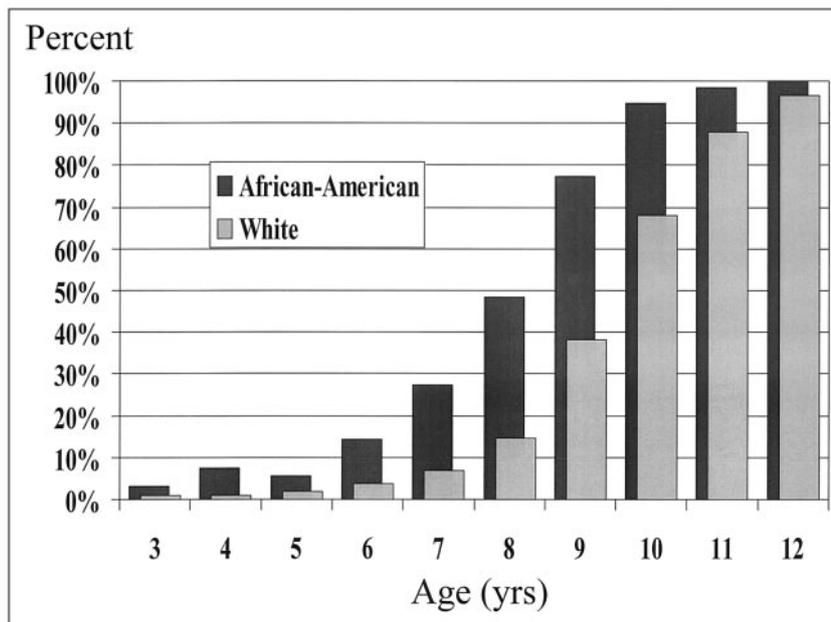


FIGURE 1. Early development of physical signs of puberty in North American females. Prevalence of thelarche and/or pubarche at SMR (Tanner) stage II or greater by age and race in 17,077 girls. Reproduced with permission from Herman-Giddens PA, Slora EJ, Wasserman RC, et al. *Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings Network*. *Pediatrics*. 1997;99:505–512.

TABLE 3. Hormonal Changes During Sexual Development in the Female

SMR (TANNER) BREAST STAGE	LUTEINIZING HORMONE (IU/L)		FOLLICLE- STIMULATING HORMONE (IU/L)		ESTRADIOL (ng/dL)	DEHYDRO- EPIANDROSTERONE SULFATE (mcg/dL)
	BASAL	POST- GnRH	BASAL	POST- GnRH		
I	0.03±0.03	2.0±1.5	2.16±1.14	21±5.5	0.8 (0.5–2.0)	40 (19–114)
II	0.71±1.04	21±17	3.44±1.58	10±5.0	1.6 (1.0–2.4)	72 (34–129)
III	2.10±2.33		4.88±2.11		2.5 (0.7–6.0)	88 (32–226)
IV	3.67±2.22	33±20	6.19±2.55	11±3.3	4.7 (2.1–8.5)	120 (58–260)
V	2.88±2.68		4.92±2.31		11 (3.4–17)	148 (44–248)
Adult	5.76±3.46		6.63±2.19		Foll 5.2 (3–10) Lut 13.0 (7–30)	153 (60–255)

Data from Neely EK, Hintz RL, Wilson DM, et al. Normal ranges for immunochemiluminometric gonadotropin assays. J Pediatr. 1995; 127:40–46. The gonadotropin assays employed in this manuscript are ultrasensitive; the standards were human pituitary luteinizing hormone 80/522 and follicle-stimulating hormone 83/575. GnRH=gonadotropin-releasing hormone; ±=1 standard deviation; (range); Post-GnRH SMR (Tanner) stage II & III and IV & V combined data

TABLE 4. Hormonal Changes During Sexual Development in the Male

SMR (TANNER) GENITAL STAGE	LUTEINIZING HORMONE (IU/L)		FOLLICLE- STIMULATING HORMONE (IU/L)		TESTOSTERONE (ng/dL)	DEHYDRO- EPIANDROSTERONE SULFATE (mcg/dL)
	BASAL	POST- GnRH	BASAL	POST- GnRH		
I	0.70±0.97	3.2±3.0	2.52±1.83	4.7±2.2	4.9 (<3–10)	36 (13–83)
II	1.80±1.30	15±6.3	2.75±1.84	3.4±2.2	42 (18–50)	93 (42–109)
III	1.86±1.41		2.94±1.55		190 (100–320)	122 (48–208)
IV	2.65±1.81	42±23	4.47±1.88	11±5.6	372 (200–620)	206 (102–385)
V	2.76±1.12		7.64±2.50		546 (350–970)	230 (120–370)
Adult	4.51±1.99		4.91±2.02		627 (350–1,030)	270 (100–450)

Data from Neely EK, Hintz RL, Wilson DM, et al. Normal ranges for immunochemiluminometric gonadotropin assays. J Pediatr. 1995; 127:40–46. The gonadotropin assays employed in this manuscript are ultrasensitive; the standards were human pituitary luteinizing hormone 80/522 and follicle-stimulating hormone 83/575. GnRH=gonadotropin-releasing hormone; ±=1 standard deviation; (range); Post-GnRH SMR (Tanner) stage II & III and IV & V combined data

due to the hypometabolic state that prolongs LH and FSH biologic activity or, because thyroid-stimulating hormone also binds to LH and FSH receptors, high concentrations of this hormone may simulate gonadotropin function. In females, primary hypothyroidism may be associated with multiple, large ovarian cysts that occasionally twist and infarct the ovary. Primary hypothyroidism is accompanied by hyperprolactinemia and occasionally by galactorrhea in both genders.

Incomplete forms of isosexual precocious puberty are relatively benign. As noted, the HPG axis is active even in prepubertal girls; if an ovarian follicle secretes sufficient estrogen, breast and uterine endometrial growth may be stimulated, leading to premature thelarche or uncommonly premature menarche, which are both self-limited and non-progressive states. Postnatally, in utero breast development usually disappears within several weeks

after birth, but occasionally it may persist for as long as 8 months. Approximately 10% of children who have apparent premature thelarche progress to CPP, particularly if breast growth begins after 2 years of age. Premature pubarche, which most often is due to an early increase in adrenal androgen secretion (premature adrenarche), is followed by functional ovarian hyperandrogenism in 20% of affected young women.

TABLE 5. Causes of Isexual Precocious Puberty

True and Complete (Central) Precocious Puberty
<ul style="list-style-type: none"> • Idiopathic: With/without hypothalamic hamartoma
<ul style="list-style-type: none"> • Secondary <ul style="list-style-type: none"> —Congenital anomalies: hamartoma, hydrocephalus, arachnoid or ventricular cyst, septo-optic dysplasia, empty sella syndrome, myelomeningocele —Postinflammatory: encephalitis, meningitis, abscess, granulomatous disease —Radiation therapy —Trauma —Neoplasms: hypothalamic hamartoma, astrocytoma, ependymoma, glioma (neurofibromatosis), craniopharyngioma
<ul style="list-style-type: none"> • Following effective treatment of long-standing pseudoisosexual precocity
Pseudoisosexual Precocious Puberty
<ul style="list-style-type: none"> • Familial male-limited precocious puberty
<ul style="list-style-type: none"> • McCune-Albright syndrome
<ul style="list-style-type: none"> • Gonadal/extragenital tumors <ul style="list-style-type: none"> —Estrogen-secreting: ovarian cyst, granulosa cell, calcifying Sertoli cell tumors, Peutz-Jeghers syndrome —Testosterone-secreting: Leydig cell, teratoma —Human chorionic gonadotropin-secreting: hepatoblastoma, germinoma, choriocarcinoma
<ul style="list-style-type: none"> • Adrenal <ul style="list-style-type: none"> —Congenital adrenal hyperplasia: 21-hydroxylase, 11β-hydroxylase deficiency —Adenoma, carcinoma —Glucocorticoid resistance
<ul style="list-style-type: none"> • Exogenous sex hormones
<ul style="list-style-type: none"> • Primary hypothyroidism
Incomplete Precocious Puberty
<ul style="list-style-type: none"> • Premature thelarche
<ul style="list-style-type: none"> • Premature menarche
<ul style="list-style-type: none"> • Premature pubarche/adrenarche

Evaluation

CLINICAL EVALUATION

A thorough historical review and complete physical examination are the first steps in evaluating the child who has precocious puberty (Table 6, Figs. 2 and 3). If the primary concern is early thelarche, it is helpful to determine whether neonatal breast development has persisted or regressed only to recur later; the latter suggests a “new” process. The growth rate in the child who has CPP or pseudoisosexual precocious puberty usually is rapid, and height rises to a higher growth percentile than occupied previously. Children

who have incomplete forms of precocious puberty usually continue to grow steadily in an established channel. It is essential to learn if a sibling had ambiguous genitalia (ie, congenital adrenal hyperplasia) or if the father, grandfather, or uncle was sexually precocious (familial male-limited sexual precocity).

Height, weight, and head circumference are plotted (increasing head circumference may suggest hydrocephalus); blood pressure is recorded (an elevated blood pressure may suggest congenital adrenal hyperplasia due to deficiency of 11 beta-hydroxylase); sexual maturity is rated; and signs of systemic

disease are sought. In girls, it is necessary to distinguish between the dense, irregular consistency of ductal breast tissue and the soft, smooth consistency of increased subcutaneous fat and between the reddish, less moist vaginal mucosa and small labia minora of the prepubertal girl compared with the pale, moist appearance of pubertal vaginal mucosa and elongated labia minora. In boys, measurement of phallic and testicular dimensions and careful palpation of the testes are crucial; testicular volume is disproportionately greater than phallic size, as in normal puberty, in males who have CPP (and some who have primary hypothyroidism). In males who have pseudoisosexual precocious puberty, penile dimensions are disproportionately greater than testicular size. Usually the testes are prepubertal in size (long diameter \leq 2 cm, volume \leq 3 mL) and consistency (indicative of an extragonadal source of androgen such as the adrenal or a teratoma). Sometimes they may be modestly and symmetrically enlarged (2.5 to 3.5 cm, 5 to 6 mL) (familial male-limited precocious puberty, hCG-secreting tumors), and rarely they are asymmetrically enlarged, possibly with the presence of a palpable mass (Leydig cell or adrenal rest tumor). In girls who have isolated vaginal bleeding, it is necessary to exclude local causes, such as a foreign body, vaginitis, and neoplasia.

LABORATORY ASSESSMENT

The next step in the evaluation is governed by the physical findings and the child’s bone age (hand/wrist radiograph) (Figs. 2 and 3). Advanced skeletal maturation reflects long-standing sex hormone action and possible developmental maturity of the CNS and HPG axis. In most patients who have CPP or pseudoisosexual precocious puberty, the bone age is more than 2 years in advance of the chronologic age. In children who have incomplete forms of precocious puberty, bone age more closely approximates or is only slightly more mature than the chronologic age. When the diagnosis of the McCune-Albright syndrome is suspected, a skeletal survey or tech-

TABLE 6. Evaluation of the Child Who Has Precocious Puberty

History	
• Patient:	Pubertal sign(s), age at onset, rate of progression, growth pattern
• Family:	Patterns of sexual maturation in first- and second-degree relatives, isosexual or heterosexual precocious puberty in other members
• Past medical:	Insults to the central nervous system, exposure to environmental sex hormones, serious illnesses or untoward symptoms
Physical Examination	
• Vital signs:	Height, weight, head circumference, blood pressure
• General:	Signs of specific illness—eg, café-au-lait spots, myxedematous face, thyromegaly, abnormal visual fields, abnormal neurologic findings
• Maturation:	SMR (Tanner) stage(s) of sexual development; in males, size, consistency, symmetry of testes in relationship to phallic size; in females, maturation of external genitalia

netium bone scan may reveal polyostotic fibrous dysplasia. Thyroid function is assessed in children in whom primary hypothyroidism is suspected.

Basal levels of LH, FSH (hCG if a germinoma is suspected), and sex hormones (testosterone in boys, estradiol in girls) are measured in patients who have possible CPP or pseudoisosexual precocity (Table 7). In girls who have isosexual precocity, basal LH levels in excess of 0.3 IU/L are found primarily in CPP. If necessary, the prepubertal or pubertal state of the HPG axis may be assessed further by determining the gonadotropin secretory response to GnRH. A serum LH concentration of 8 IU/L 40 minutes after the subcutaneous administration of 100 mcg of GnRH is consistent with CPP. Suppressed or prepubertal GnRH-stimulated LH secretion is consistent with either pseudoisosexual or incomplete forms of sexual precocity. However, as with all gonadotropin assays, there is overlap between basal and post-GnRH LH and FSH values among prepubertal and early pubertal subjects. Therefore, basal and post-GnRH LH and

FSH measurements must be interpreted in relation to the clinical findings, bone age, and sex hormone levels.

Basal serum concentrations of estradiol frequently are low (<10 pg/mL) or appropriate for the SMR (Tanner) stage of breast development in girls who have CPP; in those who have estrogen-secreting ovarian cysts or granulosa cell tumors, estradiol levels often exceed 100 pg/mL. Serum concentrations of anti-müllerian hormone often are increased in patients who have ovarian granulosa cell tumors. Ultrasensitive assays for estrogen are being developed that may help distinguish between prepubertal girls and those who have various forms of precocious puberty. In girls who have CPP, pelvic ultrasonography reveals a maturational increase in uterine length and ovarian volume and echogenic pattern (>6 cysts >4 mm in diameter). Ovarian cysts are demonstrated easily by this technique unless the cyst has ruptured and disappeared by the time of the examination. Because it is difficult to interpret pelvic ultrasonograms in prepubertal and pubertal girls, the

reader should be experienced. In boys who have CPP, serum testosterone values are appropriate for the SMR (Tanner) stage of male genital development and substantially elevated in those who have testicular neoplasms. Magnetic resonance imaging of the CNS is essential in all patients who have CPP to identify any specifically treatable CNS lesion.

Boys who have 21-hydroxylase-deficient congenital adrenal hyperplasia will exhibit elevated serum concentrations of 17 alpha-hydroxyprogesterone that decline after administration of cortisol. In those who have deficiency of 11 beta-hydroxylase, serum levels of 11-deoxycortisol are increased. Patients who have virilizing adrenal tumors have markedly elevated serum levels of DHEA and DHEAS. Those who have familial male-limited precocious puberty often present with a positive family history, symmetrically but only slightly (5 to 6 mL) enlarged testes, pubertal serum testosterone levels that increase further after hCG administration, prepubertal basal and post-GnRH concentrations of LH and FSH, and testosterone secretion that is not suppressible by GnRH agonists. Leydig cell tumors usually are identified as unilateral testicular masses; testosterone concentrations are pubertal and nonsuppressible.

In children who have premature thelarche (or rarely, premature menarche), the bone age is similar to or only modestly advanced (<2 y) over chronologic age; serum levels of LH, FSH, and estradiol are within the prepubertal ranges; and pelvic ultrasonography reveals prepubertal uterine and ovarian sizes and echogenic patterns (<3 cysts <5 mm in diameter). Clinical judgment dictates the extent of evaluation of a female infant who has suspected premature thelarche, with watchful observation often being the most appropriate. For girls who have vaginal bleeding for which a local cause cannot be identified readily, pelvic ultrasonography is required to eliminate an intravaginal neoplasm.

For children who have premature pubarche, bone age is usually less than 2 years in advance of chrono-

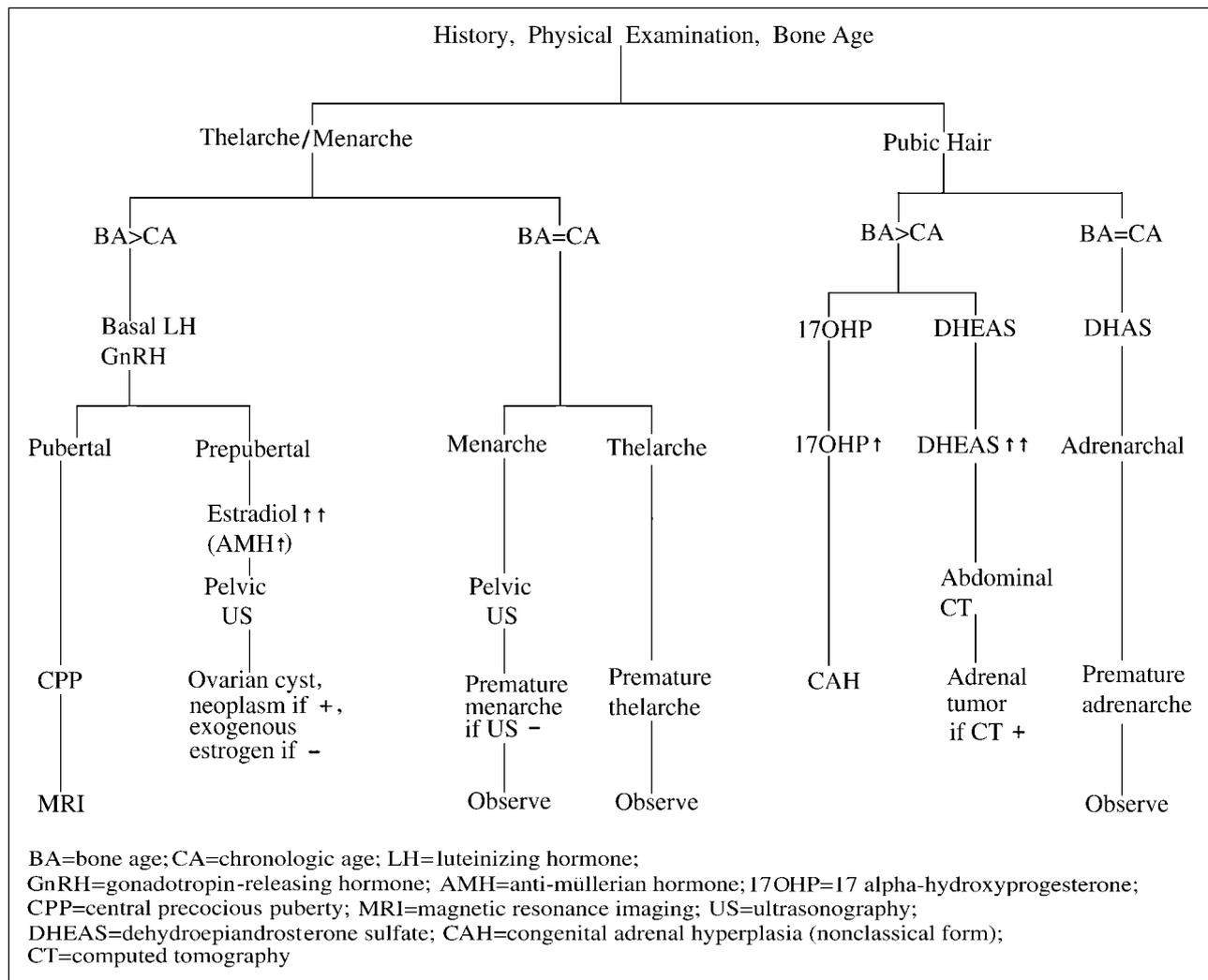


FIGURE 2. Evaluation of the female who has isosexual precocious puberty.

logic age, growth rate is not increased markedly, and DHEA (>50 ng/dL) and DHEAS (>20 mcg/dL) levels are within adrenarchal ranges. Only rarely does a child who has premature pubarche have a nonclassical form of 21-hydroxylase-deficient congenital adrenal hyperplasia. If the growth rate is unduly rapid and the bone age is more than 2 years in advance of chronologic age (particularly if there is clitoral or penile enlargement), it is appropriate to measure the basal concentration and post-adrenocorticotropin (intravenous bolus of ACTH 0.25 mg followed by sampling at >60 min) secretory response of 17 alpha-hydroxyprogesterone. Mutations in 3 beta-hydroxysteroid dehydrogenase are extremely rare in patients who have premature adrenarche.

Management and Prognosis

Effective management of the child who has isosexual precocious puberty depends on accurate identification of the cause and assessment of its significance. In children who have CPP due to a specifically remediable anatomic abnormality of the CNS, primary attention is focused on management of the underlying disorder; the effect of its successful treatment on the course of CPP then is monitored because this process may ameliorate.

IDIOPATHIC CPP

In those who have idiopathic CPP or puberty associated with a hypothalamic hamartoma or other form of CPP for which primary therapy is not available (eg, the child who has pseudoisosexual precocity that dur-

ing or after treatment has evolved into CPP), the pubertal HPG axis may be inhibited by the administration of a long-acting agonist of GnRH (GnRHa). The most commonly employed agent is depot-leuprolide (0.3 mg/kg intramuscularly every 3 to 4 weeks). Long-acting forms of GnRHa are more effective in suppressing the HPG than are shorter-acting forms administered several times daily by intranasal inhalation or subcutaneous injection.

The use of GnRHa (a stimulus to LH and FSH secretion) in children who have CPP may seem paradoxical because an intravenous pulse of GnRH stimulates gonadotropin secretion. However, when GnRH is administered as a constant infusion over several hours, gonadotropin secretion initially is stimulated and

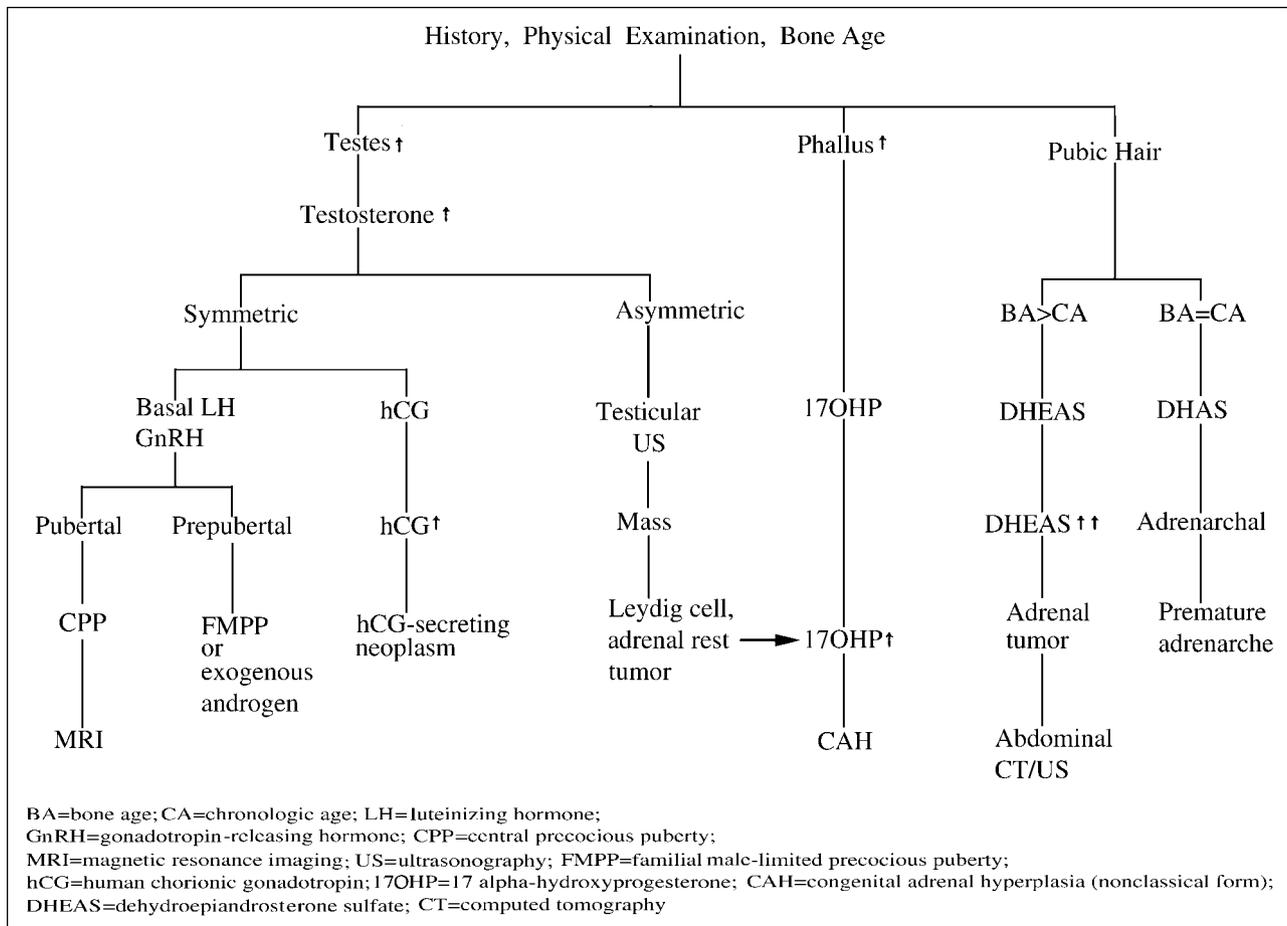


FIGURE 3. Evaluation of the male who has isosexual precocious puberty.

TABLE 7. Maximum Basal and Peak Post-GnRH Gonadotropin Concentrations (Immunochemiluminometric Assays) in Prepubertal Males and Females

	LUTEINIZING HORMONE (IU/L)	FOLLICLE-STIMULATING HORMONE (IU/L)
Males		
<10 y	0.15	2.2
10.1 to 12 y	2.7	6.2
Peak post-GnRH	7.9	9.1
Females (Postpubertal)		
Peak post-GnRH	5.0	32

then inhibited. This inhibition is attributed to downregulation of gonadotroph membrane GnRH receptors and alterations in intragonadotroph synthesis of the gonadotropins. The same process occurs when long-acting GnRHa is administered by intramuscular injection.

In some girls who have CPP,

vaginal bleeding may occur 2 weeks after the first injection of GnRHa but usually not thereafter. In the majority of children who have CPP, suppression of HPG function is complete within 4 to 8 weeks after initiation of therapy. The continued efficacy of GnRHa therapy is monitored clinically (decline in growth

rate, regression or lack of progression of physical signs of sexual maturation, amenorrhea), radiographically (decreased rate or even arrest of bone age advancement), and hormonally (basal estradiol or testosterone and post-GnRH peak LH concentrations at 3-month intervals).

Although GnRHa effectively suppresses HPG function in children who have CPP, it is important to identify the child in whom treatment is necessary and appropriate. Most boys who have CPP merit therapy with GnRHa because their bone age usually is markedly advanced and pubertal development is progressive. For many girls who have CPP, sexual maturation progresses slowly; their bone age is not greatly in advance of chronologic age, the change in the height age/bone age ratio is >0.9 per year, growth rate is normal, and predicted adult height is compatible with genetic potential and does not decline during observation. In such children, reassurance and observation as they fade into

early-normal puberty are appropriate. Nevertheless, it is necessary to follow all girls who have CPP because occasionally a child who has the apparently slowly progressive form may experience rapid acceleration of skeletal maturation and develop criteria for treatment with GnRHa.

Several questions should be considered before placing the child who has CPP on GnRHa (Table 8). If the majority of answers to these questions are positive, treatment with GnRHa should be initiated. Depending on the age, skeletal maturation, and hormonal data, it often is reasonable to follow the girl who has idiopathic CPP for 6 months to document the rate of pubertal progression before deciding whether GnRHa therapy is appropriate.

Administration of GnRHa leads to cessation of menses in girls and

regression or halt in the progression of sexual characteristics in both genders. The rates of linear growth and skeletal maturation decline. With GnRHa treatment, the adult height of children who have CPP now is 8 to 12 cm greater than that realized before the availability of this therapeutic agent. Trials of combined administration of GnRHa and growth hormone have been initiated with initially encouraging increases in predicted adult height. However, the long-term effects of combined treatment on achieved adult height and psychosocial advantage that it may provide have yet to be defined. Therapy with GnRHa usually is halted between 11 and 12 years of age in girls and 12 and 13 years of age in boys as age peers achieve their pubertal development. After discontinuing GnRHa, the HPG rapidly returns to the pubertal state; menses usually occur within 6 to 18 months after stopping GnRHa injections.

may be treated effectively with GnRHa.

PREMATURE THELARCHE AND ADRENARCHE

In the majority of girls who have premature thelarche, breast growth regresses within 4 years after it first developed. However, CPP evolves in approximately 10% of children who have apparent premature thelarche. Girls who have premature thelarche may have several monthly menstrual periods before menses disappear. In general, the parents of these girls may be reassured and the child observed. Most boys and many girls who have premature adrenarche experience no long-term adverse effects; because of the high frequency (20%) of functional ovarian hyperandrogenism, all girls who have premature adrenarche require follow-up into young adulthood.

PSYCHOSOCIAL ASPECTS

Children, particularly boys, who have markedly advanced sexual development tend to be shy and withdrawn when in the company of their age peers and may seek older companions. Because of their large size and mature physical appearance, more advanced sexual and maturational behavior may be expected from such children by adults. However, the intellectual, emotional, psychosocial, and psychosexual development of these children usually is age-appropriate. It is essential to provide counseling and support to parents and teachers in regard to the need to expect age- (not appearance-) appropriate behavior. It also is crucial to provide safeguards to prevent sexual abuse of the child who has CPP and is potentially fertile. There appear to be few long-term adverse psychosocial or educational consequences of isosexual precocity. When pubertal advance is halted or regresses during GnRHa treatment, some of the behavioral concerns also recede.

SUGGESTED READING

Eckert KL, Wilson DM, Bachrach LK, et al. A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. *Pediatrics*. 1996;97:517-519

PSEUDOISOSEXUAL PRECOCIOUS PUBERTY

In patients who have pseudoisosexual precocious puberty, the primary disease must be treated. Gonadal, adrenal, and other tumors are excised; patients who have classical and nonclassical forms of congenital adrenal hyperplasia receive cortisol; and those who have hypothyroidism are treated with thyroxine. Ovarian cysts associated with thelarche and elevated estrogen levels may be managed expectantly; the cyst often regresses spontaneously. In boys who have familial male-limited precocious puberty or the McCune-Albright syndrome, testosterone synthesis may be inhibited by ketoconazole (an inhibitor of 17 alpha-hydroxylase/17-20 lyase). Testolactone, an aromatase inhibitor, may be useful temporarily in girls who have hyperestrogenemia due to the McCune-Albright syndrome. After suppression of gonadotropin-independent sex hormone secretion, some patients who have pseudoisosexual precocious puberty may have the condition evolve into CPP, particularly if their bone ages are in the pubertal range. These children then

TABLE 8. Assessment of Female Candidates for Agonist of Gonadotropin-releasing Hormone Therapy

1. Is puberty truly premature?
2. Does the child have central precocious puberty?
3. Are the physical signs of puberty and the rate of skeletal maturation progressing rapidly and, thus, likely compromising adult height (ie, predicted adult height more than 2 standard deviations below population mean or the midparental target height)?
4. Is the child also deficient in growth hormone?
5. Has psychosocial well-being been compromised?
6. Is treatment likely to improve the quality of life?
7. Are the anticipated gains worth the potential (albeit limited) complications of therapy?

Adapted from Rosenfield RL. Selection of children with precocious puberty for treatment with gonadotropin releasing hormone analogs. J Pediatr. 1994;124:989-991.

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PIR QUIZ

Quiz also available online at www.pedsinreview.org.

5. A 12-year-old African-American girl is brought to you because her parents are concerned about her advanced sexual maturation. She has been menstruating for the past 6 months. Physical examination reveals sexual maturity rating (SMR) (Tanner) stage IV development for breasts and pubic hair. There is mounding of the areolae above the plane of both breasts. Pubic hair is adult in character and confined to the mons. Which of the following is the *most* appropriate next step?
 - A. Early morning measurement of luteinizing hormone (LH).
 - B. Gonadotropin-releasing hormone (GnRH) challenge tests.
 - C. Magnetic resonance imaging of the brain.
 - D. Pelvic ultrasonography.
 - E. Reassurance that this is normal development.
6. Which of the following statements regarding central precocious puberty (CPP) is *true*?
 - A. A structural abnormality of the central nervous system is more likely to be encountered in girls than in boys.
 - B. Bone age corresponds with chronologic age in boys who have CPP.
 - C. Germ-line mutation in the LH receptor, resulting in increased Leydig cell testosterone synthesis, is present in some boys who have CPP.
 - D. The hypothalamic-pituitary-gonadal (HPG) axis is disrupted because of the impaired negative feedback mechanism.
 - E. Treatment with agonist to GnRH is more likely to be indicated in boys than in girls.
7. A 10-year-old Caucasian boy is brought to you because of the appearance of facial, axillary, and pubic hair. Physical examination reveals that both testes and the penis are enlarged to a size appropriate for SMR (Tanner) stage IV sexual maturation. Pubic hair is adult in character and is confined to the suprapubic region. Bone age is 12 years. Serum LH concentrations in a basal state and after GnRH challenge are consistent with pubertal response. Which of the following conditions could *best* explain these findings?
 - A. Adrenal tumor.
 - B. Familial male-limited precocious puberty.
 - C. Hypothalamic hamartoma.
 - D. Leydig cell tumor.
 - E. Mediastinal germinoma.
8. A 9-year-old Caucasian girl is brought to you because of an increase in breast size. She has been menstruating for the past 6 months. Physical examination reveals SMR (Tanner) stage III breast and pubic hair maturation. Both breasts are symmetrically enlarged, with the breast diameter being twice the areolar width. Pubic hair is dark and coarse and confined to the mons. Bone age is 11 years. Serum LH concentrations in a basal state and after GnRH challenge are in prepubertal ranges. Serum estradiol and anti-müllerian hormone concentrations are markedly elevated. Which of the following conditions could *best* explain these findings?
 - A. Central precocious puberty.
 - B. Congenital adrenal hyperplasia.
 - C. Hyperthyroidism.
 - D. Normal variation.
 - E. Ovarian granulosa cell tumor.