

Short stature

Summary

Short stature (dwarfism) in children is defined as a height that is at least two standard deviations (SDs) below the mean for children of the same age and sex. In adults, the condition is commonly defined as a height of 5 ft 1 in (155 cm) or less in men and 4 ft 10 in (147 cm) or less in women. Nonpathological variant short stature can be classified into three types: familial short stature (inherited short stature), constitutional delay of growth and puberty (an inherited pattern of short stature during childhood that is followed by a growth spurt during puberty, typically resulting in normal adult height), and idiopathic short stature (short stature in the absence of any metabolic, endocrine, or other diagnosis). These types of short stature are most often normal variants of growth and rarely affect a child's development beyond longitudinal growth. The pathological causes of short stature are diverse and include psychosocial circumstances as well as a variety of genetic, endocrine, and metabolic disorders, which may affect a child's development in other ways than longitudinal growth. Further diagnostic testing is indicated if a child's growth is less than what might be expected given the average height of the parents. An x-ray of the left hand and wrist are made to determine bone age (skeletal age), based on which the adult size of the child can be predicted. Laboratory testing can help rule out any underlying condition. Treatment is rarely indicated in nonpathological short stature (e.g., if short stature does not represent a disability to the patient), while pathological short stature is treated according to the underlying condition and usually involves growth hormone supplementation.

A. General concepts

- Definition.** Short stature is defined as height that is 2 standard deviations (SDs) below the mean height of the population (i.e., below the third percentile), or 2 SDs below the midparental height (MPH).
 - Normal variant short stature** describes a child with short stature and a normal growth velocity.
 - Pathologic short stature** describes a child with short stature and a suboptimal growth velocity.
- Key point:** It is critical to evaluate growth velocity and not just absolute height when evaluating short stature. Growth velocity is ideally calculated over at least a 6-month period. Using measurements collected over a shorter period of time may result in inaccurate growth velocity calculations.
- Key point:** Children who grow 2 inches per year (5 cm per year) between 3 years of age and puberty usually do not have an endocrinopathy or underlying pathologic disorder.
- In the first 2 years of life, a downward shift in the height percentile is not uncommon and may reflect familial (or genetic) short stature, or constitutional delay of growth and puberty (CDGP).
- All patients with short stature who are more than 2 SDs below the mean or who have a growth velocity less than 5 cm per year are considered to have a pathologic growth disorder until proven otherwise.
- Determining the targeted MPH** is important in evaluating all patients with short stature (Figure 6-1).
 - Most children, when they have completed their growth, are within ± 2 SDs, or 4 inches, of their MPH.
 - A major discrepancy between a child's present growth percentile and the targeted MPH percentile suggests a pathologic state.

PHASES OF GROWTH

- Infantile:** growth during this period is about 30-35cm. Infants often cross percentile lines in the first 24 months as they grow toward their genetic potential and get further away from the excesses or constraints of the intrauterine environment.
- Childhood:** Characterized by growth at a relatively constant velocity of 4.8-6 cm/y.
- Pubertal:** Growth spurt of 8-14cm/y due to synergistic effects of increasing gonadal steroid and growth hormone secretion.

PREDICTION OF HEIGHT POTENTIAL

- An estimate of a child's adult height potential can be obtained by calculation of the midparental height, adjusted for the sex of the child.
- For girls, 13cm is subtracted from the father's height and averaged with the mother's height.
- For boys, 13cm is added to the mother's height and averaged with the father's.
- In general, the rule of "fives" for length or height should suffice to estimate normal growth.

	BIRTH	1Y	4Y	8Y	12Y
LENGTH OR HEIGHT	50	75	100	125	150
GROWTH VELOCITY		25	10	5	5

B. History

1. **Perinatal history.** Assess for prematurity or intrauterine growth retardation (**IUGR**) or small for gestational age (**SGA**). A history of neonatal hypoglycemia, prolonged jaundice, and/or microphallus suggests **hypopituitarism resulting in growth hormone (GH) deficiency**.
2. **Chronic diseases** such as **hypothyroidism**, **renal failure**, central nervous system (**CNS**) **disease**, severe asthma with frequent and prolonged steroid use, sickle cell anemia, celiac disease, and inflammatory bowel disease may manifest as short stature.
3. **Chronic use of drugs**, such as **steroids** or **stimulants for attention deficit/hyperactivity disorder**, that result in significant appetite suppression and poor weight gain may lead to short stature.
4. **Family history, especially parental growth and pubertal histories, is important.** To evaluate for constitutional delay of growth and puberty, or CDGP [see [section I.D.1](#)], ask whether the family history is positive for males with “late growth spurts” in high school or college and the age of maternal menarche.
5. **Social history** is critical because children who live in neglected or hostile environments may exhibit short stature because of **psychosocial deprivation**.
6. **Review of systems** should include questions about cold intolerance and constipation (hypothyroidism), abdominal pain, diarrhea or bloody stools (inflammatory bowel disease), and headaches and vomiting (brain tumor).
7. **Dental history.** Delayed dental eruption may suggest CDGP or GH deficiency.

C. Physical examination

1. **Accurate height and weight** should be plotted on a US National Center for Health Statistics (NCHS) growth chart, along with previous growth points, to assess the child's growth pattern. The MPH should be noted on the growth chart.
2. **Measure the patient's upper-to-lower (U/L) body segment ratio.**
 - a. **Lower segment** = pubic symphysis to the heel
 - b. **Upper segment** = total height minus lower segment
 - c. **Normal ratios**
 1. Birth = 1.7
 2. 3 years of age = 1.3
 3. >7 years of age = 1.0
 - d. **Abnormal U/L ratio** suggests **disproportionate short stature** [see [section I.D.2.b](#)].
3. Thorough physical examination should include a funduscopic examination, assessment for midline defects (central incisors, cleft palates, etc.), assessment of thyroid size, evaluation for stigmata of genetic syndromes (e.g., web neck, shield chest, and abnormal carrying angles are suggestive of Turner syndrome; see Chapter 5, section IV.C.1), scoliosis screening, and Tanner staging (see Chapter 3, section I.A.2).

D. Categorization of short stature (Figure 6-2)

1. **Normal variant short stature** refers to children with **short stature and normal growth velocity**. The two most common categories of normal variant short stature are **familial** (or genetic) short stature and **CDGP**.
 - a. **Familial (or genetic) short stature** is defined as a height at least 2 SDs below the mean but within 2 SD of MPH with a **normal bone age, a normal onset of puberty, and a minimum growth velocity of 2 inches (or 5 cm) per year**.
 - b. **Constitutional delay of growth and puberty (CDGP)** is defined as short stature with a *delayed bone age, late onset of puberty and a minimum growth velocity of 2 inches (or 5 cm) per year*.

Differential features of familial short stature and constitutional delay of growth and adolescence

Feature	Familial short stature	Constitutional Delay
Parents' stature	Small (one or both)	Average
Parents' puberty	Usual timing	Delayed
Birth length	Normal	Normal
Growth (0 to 2 years)	Normal	Normal to slow
Growth (puberty)	Normal	Slow
Bone age	Normal	Delayed
Timing of puberty	Normal	Delayed
Puberty growth rate	Lower range of normal	Diminished
Adult height	Short	Normal

2. **Pathologic short stature.** Pathologic short stature, in which height fall more than 3 SDs below the mean with **abnormal growth velocity** (i.e., growth velocity less than 2 inches [or 5 cm] per year), may be categorized as **proportionate** or **disproportionate**.

a. **Proportionate short stature** is defined as short stature with a normal U/L ratio [see section I.C.2.c]. It is important to distinguish between prenatal onset and postnatal onset.

1. **Causes of prenatal-onset proportionate** short stature include

- Environmental exposures** (e.g., in utero exposure to tobacco and alcohol)
- Chromosomal disorders** (e.g., Down syndrome, Turner syndrome)
- Genetic syndromes** (e.g., Russell–Silver syndrome, Prader–Willi syndrome; see Chapter 5, sections IV.E.5 and IV.E.2, respectively)
- Viral infection** early in pregnancy (e.g., cytomegalovirus, rubella)

2. **Causes of postnatal-onset proportionate** short stature

- Malnutrition**
- Psychosocial causes** (e.g., neglect, child abuse)
- Organ system diseases**, including gastrointestinal diseases (inflammatory bowel disease, celiac disease), cardiac diseases (cyanotic congenital heart disease), renal diseases (renal failure, renal tubular acidosis), chronic lung diseases (cystic fibrosis, asthma), and endocrinopathies (hypothyroidism, GH deficiency, and cortisol excess; see also section I.F)

b. **Disproportionate short stature** is defined as short stature in patients who are short legged with an increased U/L ratio, suggesting rickets or a skeletal dysplasia.

- Consider **rickets** in patients with frontal bossing, bowed legs, low serum phosphorus level, and high serum alkaline phosphatase [see section X.C].
- Consider some form of **skeletal dysplasia** (e.g., achondroplasia) in patients who are short with short limbs (see Chapter 5, section III.H).

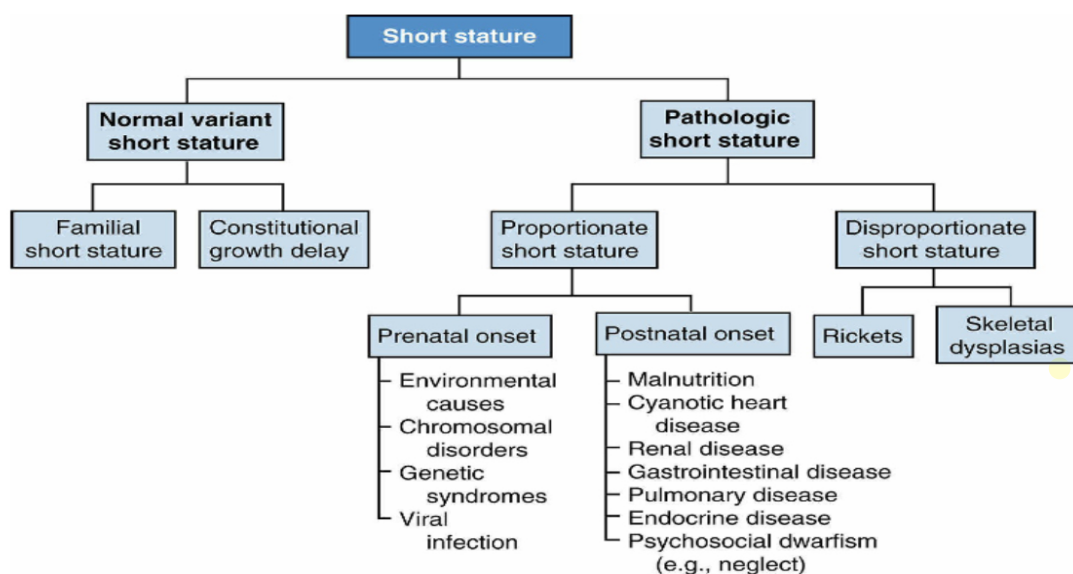


FIGURE 6.2 Differential diagnosis of short stature.

E. Evaluation of pathologic short stature

1. Laboratory studies

- Complete blood count (CBC), erythrocyte sedimentation rate (ESR), thyroxine (T_4), thyroid-stimulating hormone (TSH), tissue transglutaminase IgA (TTG IgA), total serum IgA, serum electrolytes including calcium and phosphorus, and serum creatinine and bicarbonate levels should be obtained.
- Insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGF-BP3) are indirect measures for GH deficiency. Random GH level should not be measured outside of the neonatal period, as most GH is released in a pulsatile fashion.
- Chromosome analysis in girls to evaluate for Turner syndrome
- GH stimulation testing (with agents such as clonidine or arginine) may be needed.

2. Radiographic studies

- Bone age determination (anterior–posterior [AP] film of the left hand and wrist to assess the characteristics of the epiphyses or growth plates) is helpful to compare with chronologic age (Table 6-1).
 - Neuroimaging (magnetic resonance imaging [MRI] is preferable with thin cuts through the pituitary) is appropriate if GH deficiency or concerns for other CNS pathology exist. It is not otherwise part of the routine evaluation of children with short stature.
3. **Key point:** Patients with poor growth velocity with normal screening laboratory results, but low IGF-1 and delayed bone age, should have an additional workup for GH deficiency (i.e., GH stimulation testing).

Table 6-1

Using Bone Age in the Differential Diagnosis of Short Stature

Bone Age = Chronologic Age	Bone Age < Chronologic Age
Familial short stature	Constitutional short stature
Intrauterine growth retardation	Hypothyroidism
Turner syndrome	Hypercortisolism
Skeletal dysplasia	Growth hormone deficiency
	Chronic diseases

F. Endocrinopathies that cause short stature

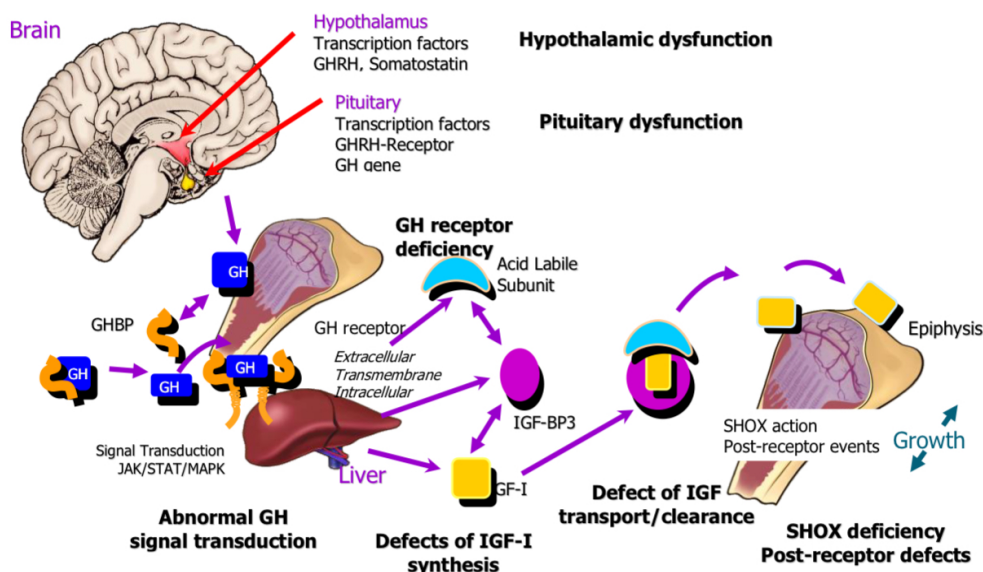
1. GH deficiency is uncommon.

- Clinical features.** A neonatal history of prolonged neonatal jaundice, hypoglycemia, micropallus, cryptorchidism, and midline defects (e.g., cleft palate) may be present. Neonates with GH deficiency are typically not SGA. Older children with GH deficiency may have obesity and cherubic facies. The growth curve demonstrates poor growth velocity (less than 2 inches or 5 cm per year).
- Causes** include brain tumors, prior CNS irradiation, CNS vascular malformations, autoimmune diseases, head trauma, and congenital midline defects. (Consider GH deficiency in patients with a single central maxillary incisor or with cleft palate.)
- Evaluation**
 - Imaging studies.** See I.E.2.a and I.E.2.b. *Key point:* All patients with GH deficiency must have neuroimaging, preferably with an MRI with thin cuts through the pituitary.
 - Laboratory studies.** Low IGF-1 and IGF-BP3 levels, as well as a poor response on GH stimulation testing (with L-DOPA [L-3,4-dihydroxyphenylalanine], arginine, glucagon, or clonidine)
- Management.** Treatment includes daily subcutaneous injections of recombinant GH until a bone age determination demonstrates that the patient has reached nearly maximal growth potential (by about 13–14 years of age in girls and 15–16 years of age in boys). In cases of CNS tumors, GH should not be used until the tumor has been treated.

GROWTH HORMONE DEFICIENCY

- Rarely Genetic; Occurs in 1:5000 children
- 30% Structural < 5 yrs (SOD most common) and >5 yrs due to tumor (cranio, glioma etc.)
- 70% Mostly idiopathic
- Can be associated with autoimmune conditions: rheumatoid arthritis, diabetes or can be due to meningitis or CNS trauma
- IGF-1
 - ⊗ Synthesized primarily in the liver
 - ⊗ Circulating levels of IGF-1 are related to the blood levels of GH and to the nutritional status
 - ⊗ The mitogenic actions of GH are mediated through increase in the synthesis of insulin-like growth factor.

HYPOTHALAMIC-PITUITARY-IGF AXIS: POSSIBLE SITES OF DEFECTS



2. **Hypothyroidism.** The most common cause of hypothyroidism is Hashimoto thyroiditis [see section IX.B.2.b]. Patients will present with increased TSH, low T_4 , and positive antithyroid peroxidase antibodies.
3. **Hypocortisolism.** The most common cause of hypocortisolism is iatrogenic, as a result of prolonged use of steroids [see section IV.E]. Patients present with a history of poor growth and increasing weight gain, purpuric stretch marks and a dorsal neck fat pad on examination, with delayed bone age.
4. **Turner syndrome** (see also Chapter 5, section IV.C.1). Female patients who are missing a part or all of one of the X chromosomes may present with short stature or lack of puberty. GH treatment has been shown to improve the ultimate height of these patients. **Key point:** All girls with short stature should have a karyotype, as the physical features of Turner syndrome can be subtle.

$$\text{MALE MPH} = \frac{\text{Father's height} + \text{Mother's height} + 5 \text{ inches}}{2}$$

$$\text{FEMALE MPH} = \frac{\text{Father's height} + \text{Mother's height} - 5 \text{ inches}}{2}$$

FIGURE 6.1 Determination of midparental height (MPH). Most patients, when they have completed their growth, will be within ± 2 standard deviations, or 4 inches, of the MPH. For example, if a boy has a father who is 5 feet 9 inches in height and a mother who is 5 feet in height, then the MPH is 5 feet 7 inches ± 4 inches.

Disorders of puberty

Summary

Puberty refers to the phase of development between childhood and adulthood in which complete functional maturation of the reproductive glands and external genitalia occurs. The other processes that characterize this transitional phase are the development of secondary sex characteristics, growth spurts, and psychosocial changes. The stages of development during puberty are classified according to the Tanner stages. Although there is considerable variation between individuals, puberty begins on average at the age of 11 in girls and 13 in boys. When puberty begins abnormally early it is referred to as precocious puberty and is classified into two main types: peripheral precocious puberty, which is independent of gonadotropin-releasing hormone secretion; and central precocious puberty, which involves the hypothalamo-hypophyseal axis. At the other end of the disease spectrum, puberty may be delayed or absent. This delay can be constitutional (most common), secondary to underlying conditions, or due to hypogonadism.

A. Normal puberty (see also Chapter 3, section I.A.2)

1. In the prepubescent state, sex steroids (testosterone and estradiol) are suppressed owing to an inactive hypothalamic–pituitary–gonadal axis (HPGA).
2. Puberty begins when there is a reduction in this hypothalamic inhibition, resulting in activation of the HPGA.
3. The HPGA releases gonadotropin-releasing hormone (GnRH) from the hypothalamus, which binds to receptors in the pituitary gland and causes the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
4. **Female puberty.** The different stages of pubertal development are defined as follows. It is important, however, to be aware that the age of onset and subsequent course of hormonal and physical changes during puberty are variable.
 - a. Onset is between 8 and 13 years of age.
 - b. **Thelarche** is the onset of breast development as a result of the release of estrogen, and **adrenarche** is the onset of pubic or axillary hair development as a result of the release of adrenal androgens. Breast buds are usually the first sign of puberty, although in 15% of girls, pubic hair develops first.
 - c. **Menarche** is the onset of the menstrual cycle. **Menstruation** begins at 9–15 years of age, with a mean onset of 12.5 years of age.
 - d. **FSH** stimulates the ovaries to produce ovarian follicles, which in turn produce estrogen.
 - e. **LH** is responsible for the positive feedback in the middle of the menstrual cycle, resulting in the release of an egg.
 - f. **Tanner staging.** See Chapter 3, section I.A.2.c.
5. **Male puberty**
 - a. Onset is between 9 and 14 years of age.
 - b. Testicular enlargement is usually the first sign of puberty (≥ 4 mL as measured with an orchidometer or >2.5 cm in length).
 - c. Seventy-five percent of the testicular volume is the seminiferous tubules.
 - d. **FSH** in boys stimulates the Sertoli cells in the seminiferous tubules of the testes to produce sperm.
 - e. **LH** in boys stimulates the testicular Leydig cells to produce androgens, which in turn are responsible for penile enlargement and the growth of axillary, facial, and pubic hair.
 - f. **Tanner staging.** See Chapter 3, section I.A.2.c.
6. African American children may develop secondary sexual characteristics earlier than other children.
7. Moderate to severe obesity may be associated with sexual precocity.

Table 3-1
Actions of Sex Hormones in Both Males and Females

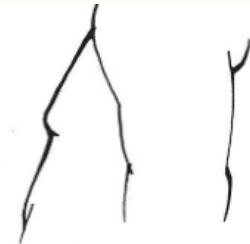
Hormone	Action in Males	Action in Females
Follicle-stimulating hormone	Induces spermatogenesis	Stimulates development of ovarian follicles Stimulates ovarian granulosa cells to produce estrogen
Luteinizing hormone	Induces testicular Leydig cells to produce testosterone	Stimulates ovarian theca cells to produce androgens Stimulates corpus luteum to produce progesterone Midcycle surge results in ovulation
Testosterone	Increases linear growth and muscle mass Induces development of penis, scrotum, prostate, and seminal vesicles Induces growth of pubic, axillary, and facial hair Deepens voice Increases libido	Stimulates linear growth Stimulates growth of pubic and axillary hair
Estradiol	Increases rate of epiphyseal fusion	Stimulates breast development Triggers midcycle luteinizing hormone surge Stimulates labial, vaginal, and uterine development Stimulates growth of a proliferative endometrium Low level stimulates linear growth High level increases rate of epiphyseal fusion
Progesterone		Converts endometrium to a secretory endometrium
Adrenal androgens	Stimulates growth of pubic hair Stimulates linear growth	Stimulates growth of pubic hair Stimulates linear growth

Tanner Stage in female:

Tanner Stages	Breast development (girls)
B1	• Prepubertal appearance and size • Occasional elevation of the <u>nipple</u>
B2	• Enlarged mammary glands form a breast bud • Slight increase in areolar diameter, <u>nipple</u> protrusion
B3	• Further enlargement of <u>mammary glands</u> • <u>Breast</u> bud extends beyond the areolar diameter
B4	• <u>Nipple</u> and areola form a secondary mound which projects above the <u>breast</u> tissue
B5	• Adult breast • <u>Areola</u> with projection of <u>papilla</u> only

Pubic hair development (boys and girls)	
Ph1	• Usually no pubic hair, <u>vellus</u> hair possible
Ph2	• Sparse, lightly pigmented <u>hair</u> (straight or curled) on the labia/base of the <u>penis</u>
Ph3	• Dark, coarse, curly <u>hair</u> spreading over the <u>pubic symphysis</u>
Ph4	• Adult pubic <u>hair</u> that does not extend to the inner thighs
Ph5	• Adult pubic <u>hair</u> that extends to the inner thighs with horizontal upper border
Ph6	• Further growth of pubic <u>hair</u> along <u>linea alba</u> in the direction of the <u>umbilicus</u>

Stage 1 Preadolescent



Stage 1 Preadolescent
No pubic hair



Stage 2 Elevation of breast and nipple as small projections



Stage 2 Sparse, long, downy hair along labia



Stage 3 Enlargement of breast
No separation of areola and breast
Areola enlarges



Stage 3 Darker, coarser, and curlier hair



Stage 4 Areola and nipple project to form secondary mound above level of breast



Stage 4 Coarse and curly adult-type hair covering symphysis pubis



Stage 5 Only nipple projects
Areola usually recedes to contour of breast
Adult breast size



Stage 5 Adult-type hair spread onto medial surface of thighs



Tanner Stage in male:

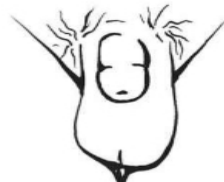
Genital development (boys)	
G1	• Prepubertal appearance and size of the <u>testes</u>, <u>scrotum</u>, and <u>penis</u>
G2	• Testicular volume of 4 mL • Larger <u>scrotum</u> • Penile growth has not begun • Scrotal <u>skin</u> darkens in color and texture
G3	• Continued enlargement of the <u>testes</u> and <u>scrotum</u> • Penile growth begins
G4	• Testicular volume of 12 mL • <u>Scrotum</u> growth • Penile growth continues: longer and wider <u>penis</u> • Development of <u>penis</u> glans
G5	• <u>Testes</u>, <u>scrotum</u>, and <u>penis</u> attain adult appearance and <u>proportions</u>

Pubic hair development (boys and girls)	
Ph1	• Usually no pubic <u>hair</u>, <u>vellus</u> <u>hair</u> possible
Ph2	• Sparse, lightly pigmented <u>hair</u> (straight or curled) on the labia/base of the <u>penis</u>
Ph3	• Dark, coarse, curly <u>hair</u> spreading over the <u>pubic</u> <u>symphysis</u>
Ph4	• Adult pubic <u>hair</u> that does not extend to the inner thighs
Ph5	• Adult pubic <u>hair</u> that extends to the inner thighs with horizontal upper border
Ph6	• Further growth of pubic <u>hair</u> along <u>linea alba</u> in the direction of the <u>umbilicus</u>

Stage 1 Preadolescent
No pubic hair
Prepubertal testes



Stage 2 Testes larger
Sparse, long, downy hair



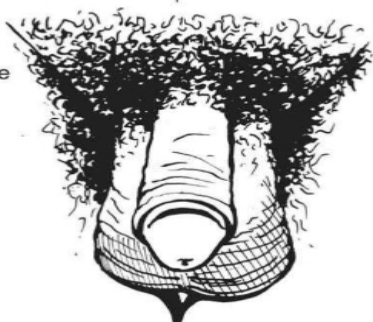
Stage 3 Testes further enlarged
Penis length enlarged
Darker, coarser, and curlier hair



Stage 4 Darkening of scrotal skin
Penis length and width increased;
glans develops
Coarse and curly pubic hair
extending over symphysis pubis



Stage 5 Testes and penis adult in size and shape
Adult-type pubic hair that spreads to
medial surface of thighs



B. Precocious puberty

1. Definitions

- a. **Girls:** presence of breast development or pubic hair before 8 years of age
- b. **Boys:** presence of testicular changes, penile enlargement, or pubic or axillary hair before 9 years of age

2. Categories

a. Premature thelarche

1. **Definition.** There is visible or palpable breast tissue only, with no other secondary sexual characteristics. The growth pattern should be normal, and no pubic hair should be apparent.
2. **Epidemiology.** This is a common and benign condition usually presenting in the first 2 years of life.
3. **Etiology.** This condition is caused by a transient activation of the HPGA, resulting in transient ovarian follicular stimulation and a release of low levels of estrogen.
4. Generally no workup is necessary as long as no other secondary sexual characteristics (clitoromegaly, pubic hair, enlarged labia minora, pink vaginal mucosa) or growth spurts are noted. Patients should be followed, and if progressive enlargement of the tissue is noted, they should be referred to a pediatric endocrinologist.

b. Premature adrenarche

1. **Definition.** Early onset of pubic or axillary hair growth without the development of breast tissue or enlarged testes.
2. **Epidemiology.** This condition is more common in girls than in boys.
3. **Classic presentation** occurs after 5 years of age, with the onset of pubic hair growth, axillary hair growth, and apocrine odor. No breast tissue or testicular enlargement is noted, and there is no clitoromegaly. Growth is normal without advancement of bone age.
4. Most patients should have a bone age radiograph, as well as laboratory testing for morning levels of 17-hydroxyprogesterone (17-OHP), as some patients with nonclassic congenital adrenal hyperplasia (CAH) may present with premature adrenarche.
5. In most cases, no treatment is indicated.

c. Central (or isosexual) precocious puberty (CPP)

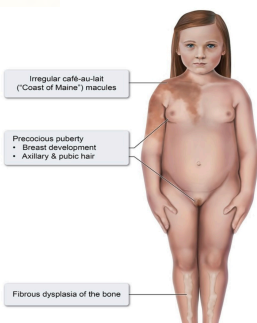
1. **Definition.** The early onset of gonadotropin-mediated (i.e., mediated by FSH and LH) puberty.
2. **Epidemiology.** Girls have a higher incidence of CPP than boys.
3. **Clinical features**
 - a. In girls, physical examination shows breast development, pubic hair, and rapid growth.
 - b. In boys, physical examination shows testicular enlargement, pubic hair, and rapid growth.
4. **Etiology**
 - a. In girls, most cases are idiopathic.
 - b. In boys, sexual precocity tends to be pathologic, and all patients need evaluation with an MRI of the head.
 - c. CNS abnormalities that may cause CPP include hydrocephalus, CNS infections, cerebral palsy, benign hypothalamic hamartomas, malignant tumors such as astrocytomas and gliomas, and severe head trauma.
 - d. Hypothyroidism may rarely present with CPP, but in this case, there is poor growth and a delayed bone age (unlike all other causes of sexual precocity in which growth is accelerated).
5. **Evaluation**
 - a. FSH, LH, and sex steroid levels are elevated. In particular, unstimulated gonadotropin testing should be done with ultrasensitive or pediatric-specific assays, and not routine LH and FSH assays that are designed for use in adults.
 - b. The GnRH stimulation test can demonstrate premature activation of the hypothalamus. Access to GnRH agonists (GnRHa) is limited in the United States; therefore, short-acting GnRHa such as leuprolide acetate

are used in stimulation tests.

1. By injecting synthetic GnRHa into a patient, the LH response, and to a lesser degree the FSH response, can be used as an assessment of the activation of the HPGA. Patients with CPP have a **dramatic increase in LH secretion** when compared with baseline levels.
2. On the other hand, prepubertal patients whose HPGA has not yet been activated, and patients with peripheral precocious puberty (PPP) in which peripherally produced sex steroids suppress pituitary gonadotropin secretion, would be expected to have a **flat response** (i.e., no increase in LH secretion) on injection of synthetic GnRHa.
- c. An MRI of the head should be performed in all boys, and in girls with any neurologic symptoms (e.g., headaches or seizures) or with rapid pubertal changes.
- d. Thyroid tests (TSH and T_4) should be performed to rule out hypothyroidism.

d. **PPP or heterosexual gonadotropin-independent puberty**

1. **Definition.** Precocious puberty that is independent of the HPGA (i.e., caused by the peripheral production of male or female sex steroids and not FSH- or LH-mediated). The hallmark of PPP is **suppressed unstimulated gonadotropin levels and/or a flat response on GnRHa stimulation testing, because the HPGA has not been activated.**
2. **Clinical features**
 - a. Boys present with either feminization (gynecomastia) or with premature onset of pubic hair. Note that there is **usually no testicular enlargement** because these patients do not have an increase in FSH, which would stimulate seminiferous tubule enlargement [see exceptions in [section II.B.2.d.\(3\).\(c\)](#)].
 - b. Girls present with typical secondary sexual characteristics or virilization.
3. **Etiology.** Causes may differ in boys and girls but, in general, include exposure to exogenous sex steroids (found in some skin lotions or foods), McCune–Albright syndrome, gonadal tumors, adrenal tumors, and nonclassic CAH; see [section IV.C.3.a.\(3\)](#). All of these causes are independent of the HPGA.
 - a. In boys, consider adrenal tumors, Leydig cell tumors (presenting with asymmetric testicular enlargement), nonclassic CAH, β -human chorionic gonadotropin (β -HCG)–producing tumors, McCune–Albright syndrome, and testotoxicosis.
 - b. In girls, consider adrenal tumors, virilizing ovarian tumors (arrhenoblastomas), feminizing ovarian tumors (juvenile granulosa tumors), nonclassic CAH, and McCune–Albright syndrome.
 - c. **Specific causes of PPP in males that result in testicular enlargement**
 1. **McCune–Albright syndrome** is characterized by fracture-prone bony changes (polyostotic fibrous dysplasia), skin findings (irregularly bordered hyperpigmented macules, or “coast of Maine” jagged-bordered café-au-lait spots), and endocrinopathies (PPP or hyperthyroidism). Patients often have enlarged gonads, but their secretion of sex steroids is independent of the HPGA.
 2. **Testotoxicosis** is a rare disease in which the testes enlarge bilaterally independent of the HPGA.
 3. **β -HCG–secreting tumors** are unique to boys. These tumors are



found in the chest, pineal gland, gonad, or liver (hepatoblastoma). Because the β -HCG molecule cross-reacts with LH, it too can bind to LH receptors and enlarge the testes slightly, stimulating Leydig cells and secreting androgens.

4. **Evaluation.** A GnRH stimulation test may be warranted in addition to the following:
 - a. **In boys,** check serum FSH, LH, testosterone, and β -HCG levels.
 - b. **In girls,** check serum FSH, LH, and estradiol levels.
 - c. Perform imaging (testicular, abdominal, CNS, etc.) studies, depending on the suspected etiology.
5. **Management.** Treatment is based on the underlying cause.

C. Delayed puberty

1. Definitions

- a. **Boys:** No testicular enlargement by 14 years of age.
- b. **Girls:** No breast tissue by 13 years of age, or no menarche by 16 years of age.

2. Classification. Two categories of disorders may result in delayed puberty.

- a. **Hypogonadotropic hypogonadism.** Because of the inactivity of the hypothalamus and pituitary gland, these patients have a low FSH, low LH, and, in turn, low testosterone and low estradiol, with a prepubertal (flat) GnRH stimulation test.
- b. **Hypergonadotropic hypogonadism.** Because of end-organ dysfunction (i.e., gonadal failure), these patients have high FSH and high LH levels with low testosterone or low estradiol levels. There is no abnormality in the hypothalamus or pituitary gland.

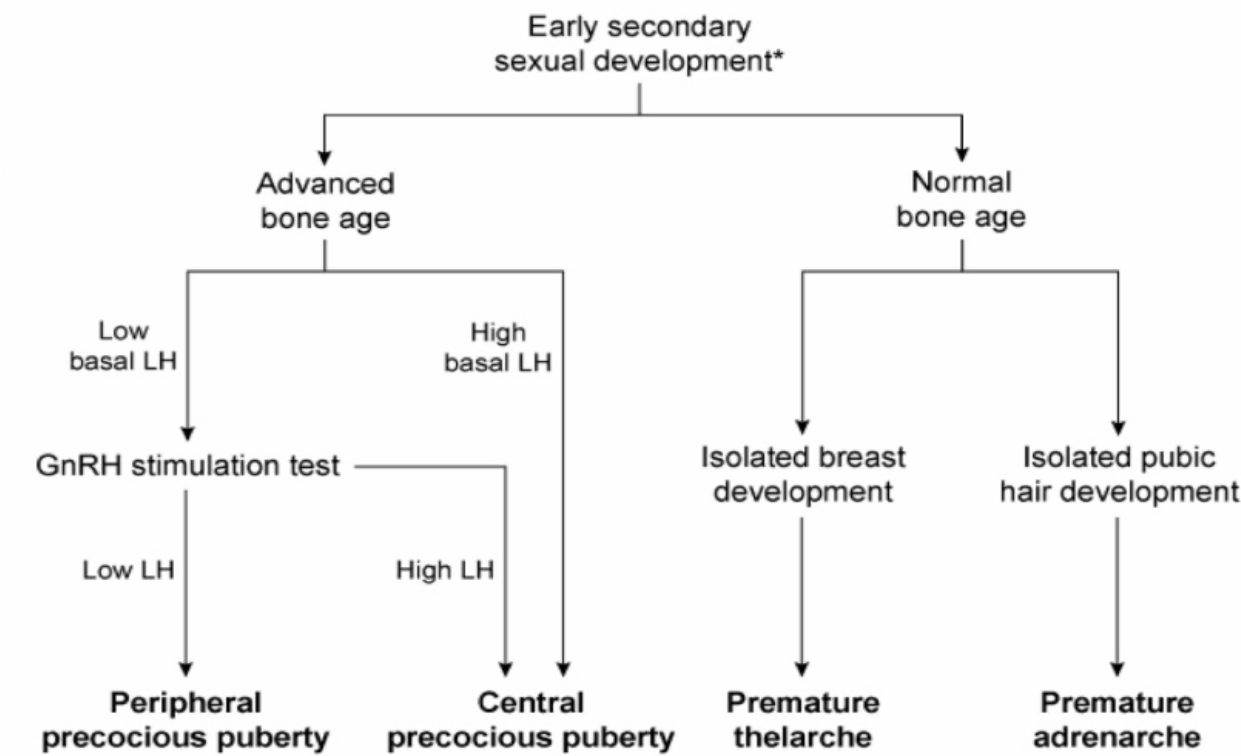
3. Etiology of hypogonadotropic hypogonadism

- a. **CDGP** (i.e., immature hypothalamus or “late bloomers”) is much more common in boys than in girls. Often there is a family history in one parent (i.e., mother had late menarche or father had his growth spurt late in high school or in college). Patients with hypogonadotropic hypogonadism frequently have CDGP [see section I.D.1.b for a description of growth pattern].
- b. **Chronic diseases** can cause pubertal delay (e.g., inflammatory bowel disease, anorexia nervosa, renal failure, and heart failure).
- c. **Hypopituitarism** of any cause (e.g., brain tumors)
- d. **Primary hypothyroidism**
- e. **Prolactinoma**
- f. **Genetic syndromes**
 1. **Kallman syndrome.** Isolated gonadotropin deficiency associated with anosmia (inability to smell)
 2. **Prader-Willi syndrome** (see Chapter 5, section IV.E.2)
 3. **Bardet-Biedl syndrome.** Obesity, retinitis pigmentosa, hypogonadism, and polysyndactyly

4. Etiology of hypergonadotropic hypogonadism

- a. **Chromosomal disorders**
 1. **In boys,** consider **Klinefelter syndrome** (XXY; see Chapter 5, section IV.C.2).
 2. **In girls,** consider **Turner syndrome** or gonadal dysgenesis (see Chapter 5, section IV.C.1).
 - b. **Autoimmune disorders** (e.g., hypogonadism in autoimmune oophoritis, which may also be associated with Hashimoto thyroiditis or Addison disease)
5. **Evaluation of delayed puberty.** A CBC, ESR, bone age, TSH and T_4 , testosterone or estradiol, FSH, LH, and prolactin levels are necessary. Neuroimaging may be warranted as well.

Evaluation of precocious puberty

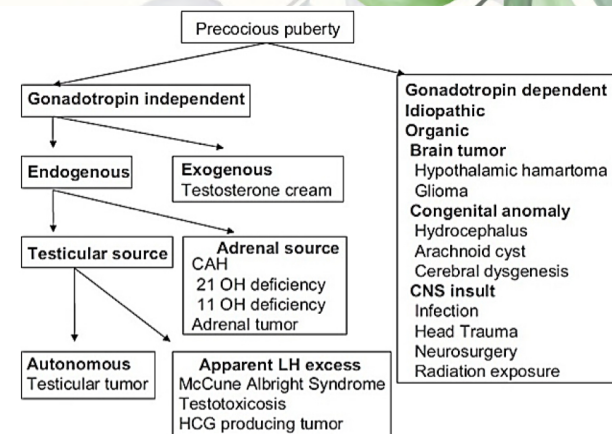


*Secondary sexual development in girls age <8 or boys age <9.

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TABLE 174.2 Differential Diagnostic Features of Delayed Puberty and Sexual Infantilism							
CAUSATIVE CONDITION/DISORDER	STATURE	PLASMA GONADOTROPINS	GNRH TEST: LH RESPONSE	PLASMA GONADAL STEROIDS	PLASMA DHEAS	KARYOTYPE	OLFACTION
Constitutional delay in growth and adolescence	Short for chronological age, usually appropriate for bone age	Prepubertal, later pubertal	Prepubertal, later pubertal	Prepubertal, later normal	Low for chronological age, appropriate for bone age	Normal	Normal
HYPOGONADOTROPIC HYPOGONADISM							
Isolated gonadotropin deficiency	Normal, absent pubertal growth spurt	Low	Prepubertal or no response	Low	Appropriate for chronological age	Normal	Normal
Kallmann syndrome	Normal, absent pubertal growth spurt	Low	Prepubertal or no response	Low	Appropriate for chronological age	Normal	Anosmia or hyposmia
Idiopathic multiple pituitary hormone deficiencies	Short stature and poor growth since early childhood	Low	Prepubertal or no response	Low	Usually low	Normal	Normal
Hypothalamic-pituitary tumors	Decrease in growth velocity of late onset	Low	Prepubertal or no response	Low	Normal or low for chronological age	Normal	Normal
PRIMARY GONADAL FAILURE							
Syndrome of gonadal dysgenesis and variants	Short stature since early childhood	High	Hyperresponsive for age	Low	Normal for chronological age	XO or variant	Normal
Klinefelter syndrome and variants	Normal to tall	High	Hyperresponsive at puberty	Low or normal	Normal for chronological age	XXY or variant	Normal
Familial XX or XY gonadal dysgenesis	Normal	High	Hyperresponsive for age	Low	Normal for chronological age	XX or XY	Normal

Disorder	Treatment	Action and Rationale
GnRH-dependent true or central precocious puberty	GnRH agonists	Desensitization of gonadotropes; blocks action of endogenous GnRH
GnRH-independent incomplete sexual precocity		
Girls		
1. Autonomous ovarian cysts	Medroxyprogesterone acetate	Inhibition of ovarian steroidogenesis; regression of cyst (inhibition of FSH release)
2. McCune-Albright syndrome	Medroxyprogesterone acetate*	Inhibition of ovarian steroidogenesis; regression of cyst (inhibition of FSH release)
	Testolactone* or fadrozole	Inhibition of P-450 aromatase; blocks estrogen synthesis
Boys		
Familial testotoxicosis	Ketoconazole*	Inhibition of P-450 _{c17} (mainly 17,20-lyase activity)
	Spironolactone* or flutamide and testolactone or fadrozole	Antiandrogen
		Inhibition of aromatase; blocks estrogen synthesis
	Medroxyprogesterone acetate*	Inhibition of testicular steroidogenesis



DIFFERENTIAL DIAGNOSIS OF SEXUAL PRECOCITY

	SERUM GONADOTROPIN CONCENTRATION*	LH RESPONSE TO GNRH	SERUM SEX STEROID CONCENTRATION	GONADAL SIZE	MISCELLANEOUS
True precocious puberty	Pubertal values	Pubertal	Pubertal values of testosterone or estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement (by sonography)	MRI scan of brain to rule out CNS tumor or other abnormality; bone scan for McCune-Albright syndrome
Incomplete sexual precocity (pituitary gonadotropin-independent)					
<i>Males</i>					
Chorionic gonadotropin-secreting tumor in males	High HCG (low LH)	Prepubertal (suppressed)	Pubertal values of testosterone	Slight to moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; MRI scan of brain if chorionic gonadotropin-secreting CNS tumor suspected
Leydig cell tumor in males	Suppressed	Suppressed	Very high testosterone	Irregular asymmetric enlargement of testes	
Familial testotoxicosis	Suppressed	Suppressed	Pubertal values of testosterone	Testes symmetric and >2.5 cm but smaller than expected for pubertal development; spermatogenesis may occur	Familial; probably sex-limited, autosomal dominant trait
Premature adrenarche	Prepubertal	Prepubertal	Prepubertal testosterone; DHEAS values appropriate for pubic hair stage 2	Testes prepubertal	Onset usually after 6 yr of age; more frequent in brain-injured children
<i>Females</i>					
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Suppressed	Very high estradiol	Ovarian enlargement on physical examination, MRI, CT, or sonography	Tumor often palpable on abdominal examination
Follicular cyst	Suppressed	Suppressed	Prepubertal to very high estradiol values	Ovarian enlargement on physical examination, MRI, CT, or sonography	Single or repetitive episodes; exclude McCune-Albright syndrome (e.g., perform skeletal survey and inspect skin)
Feminizing adrenal tumor	Suppressed	Suppressed	High estradiol and DHEAS values	Ovaries prepubertal	Unilateral adrenal mass
Premature thelarche	Prepubertal	Prepubertal	Prepubertal or early pubertal estradiol	Ovaries prepubertal	Onset usually before 3 yr of age
Premature adrenarche	Prepubertal	Prepubertal	Prepubertal estradiol; DHEAS values appropriate for pubic hair stage 2	Ovaries prepubertal	Onset usually after 6 yr of age; more frequent in brain-injured children