Normal Pubertal Development:
Part II: Clinical Aspects of Puberty

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

1. Describe the usual sequence of pubertal development in boys and girls.
2. Describe how linear growth during puberty is related to pubertal stage.
3. Identify pubertal abnormalities that require further evaluation.

Part I of this article, which deals with the endocrine basis of puberty, was published in the June 2011 issue of Pediatrics in Review.

Stages of Puberty and Their Evaluation

Sexual Maturity Rating (SMR) staging of sexual development, also known as Tanner staging, provides a means of discretely documenting a child's progression through puberty by inspection. Separate scales are used for breast (female), genital (male), and pubic hair (both sexes) development (Figs. 1 and 2). (1)(2)(3) By definition, SMR stage 1 is prepubertal. Pubertal development of the gonads is indicated specifically by thelarche (breast stage 2) in girls (Fig. 1) and testicular enlargement (genital stage 2) in boys (Fig. 2). Pubertal development is ongoing at stage 3, nearly complete by stage 4, and complete and adultlike at stage 5.

The limitation of the SMR system is that defining early breast and testicular developmental stages accurately requires palpation, not just visual inspection. (4)(5) Inspection of breast development does not enable the distinction between breast tissue development and fat deposition (adipomastia), which is a common confounder. The distinction is best made by palpation of the subareolar breast bud. Direct measurement of testicular size by palpation is likewise preferable to the SMR genital staging system, which relies on a "gestalt" visual estimation of testicular enlargement (a follicle-stimulating hormone [FSH] effect on the seminiferous tubules) that is confounded easily by penile size, which varies constitutionally and is stimulated by androgen and obscured by obesity. A testicular long diameter of >15/16 in (volume >3.0 mL, direct determination of which requires an orchidometer measurement (6))† indicates entry into puberty and is the key feature of genital stage 2 (Fig. 2). (7)(8)(9)(10) Mature pubertal testicular development (stage 5) is indicated by attainment of a testicular long diameter of 1.5 to 2.0 in (12 to 27 mL). (3)(9)(11) Testicular volume determined by ultrasonography is about half of that determined by orchidometry but correlates highly. (10)

Pubarche is not specific evidence of pubertal function of the gonads because these changes may result from either gonadal or adrenarchal androgen production. Although pubic hair stage 2 may indicate early sexual hair growth, it also may result from generalized hypertrichosis. Thus, pubic hair stage 2 is a less accurate indicator of pubertal androgen production than pubic hair stage 3, the appearance of frank sexual hair (Fig. 1). (4) Although pubic hair stages 2 to 4 may result solely from adrenarchal androgens in both sexes, the development of a "male escutcheon" (stage 6, Fig. 2), ie, sexual hair extending up the linea alba, specifically suggests a concentration of androgen above that normally found in females.

Abbreviations

BMI:	body mass index
DHEAS:	dehydroepiandrosterone sulfate
FSH:	follicle-stimulating hormone
HPG:	hypothalamic-pituitary-gonadal
PCOS:	polycystic ovary syndrome
SD:	standard deviation
SMR:	Sexual Maturity Rating

Normal Age of Attainment and Sequence of Pubertal Milestones

The normal age of onset of puberty traditionally is considered to be between 8.0 and 13.0 years in the general

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†orchidometer dimensions=ellipsoid of revolution: volume=0.52×length×(0.64×length)^2.

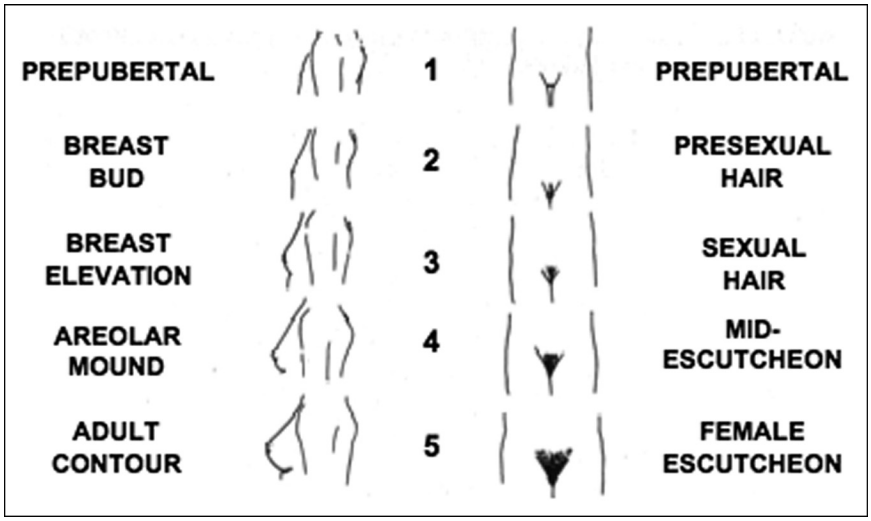

Figure 1. Stages of breast and pubic hair development. Stage 1 is prepubertal. Breast stages (left panel): 2–a subareolar breast bud, 3–elevation of the breast contour and enlargement of the areolae, 4–the areolae form a secondary mound above the contour of the breast, 5–mature female breast with recession of the secondary mound and a dependent breast contour. Pubic hair stages (right panel): 2–sparse, fine, straight pubic hair; 3—long, dark, curly hair; 4–pubic hair resembles adult pubic hair in quality but not distribution, having not yet spread to the thighs; 5–pubic hair has adult quality and distribution, with spread to the medial thighs. Males go through the same pubic hair stages and on to stage 6 (male escutcheon, an inverted triangular extension of pubic hair up the midline) at maturity (Fig. 2). Modified from Rosenfield, et al. (2008) (1) Copyright © 2005, Elsevier. A photographic atlas of pubertal stages with full descriptions is available from the American Academy of Pediatrics. (3)

population of girls and 9.0 and 14.0 years in boys. (12) Current best estimates of the ages of attainment of the key milestones in pubertal development of normal girls and boys in the general population, based on data collected from 1988 to 1994, indicate that these milestones remain appropriate (Table 1). (4) Fewer than 5% of the general population of normal-weight girls in the United States enter puberty before 8.0 years of age. However, thelarche in normal-weight girls occurs about 1 year earlier in non-Hispanic African American and Mexican American girls than in non-Hispanic white girls. Consequently, breast development is normal during the seventh year in these minority groups, about 15% of whom experience thelarche by 8.0 years of age. Sexual (stage 3) pubic hair, on the other hand, occurs in fewer than 5% of girls younger than 8.0 years of age, regardless of ethnicity.

However, there is considerable uncertainty about the current exact range of normal. The trend toward earlier age of puberty onset in girls appears to have been continuing over the past several decades, (13)(14)(15) but methodologic obstacles have hindered establishing the extent of this finding definitively. Excess adiposity contributes to the trend by an average of about 0.5 years in girls (Fig. 3). (4)

There is more debate about the trend and effect of obesity in boys. The more recent epidemiologic studies of boys in the United States are inadequate to gauge puberty onset adequately because boys' genital development was evaluated by inspection for SMR staging rather than palpation. SMR data suggest that obesity delays the onset of male puberty, (16) but data obtained by orchidometry indicate that obesity advances the onset of puberty about 0.5 years. (9)

The sequence of progression through the pubertal stages is predictable. Female puberty typically begins with thelarche, which may be asymmetric and ordinarily precedes the onset of sexual hair by about 1.0 to 1.5 years (Table 1) (Fig. 4), (4)(11) although pubarche may occur first or simultaneously. (17) Menarche occurs approximately 2.5 years (usual range, 0.5 to 3.0 years) after thelarche, at an average age of 12.6 years in white girls and 12.1 years in African American girls of normal weight, with Mexican American girls being intermediate. (4) The pubertal growth spurt (Fig. 4) commences with early puberty and occurs over 2 to 3 years, with peak height velocity being achieved before puberty is complete. (11)(18)

Male puberty typically begins with testicular enlargement. (7) Pubarche characteristically follows, with most boys attaining SMR 3 pubic hair within 1.0 to 1.5 years after testicular enlargement (Table 1) (Fig. 4). (11) The pubertal growth spurt occurs during genital stages 3 and 4, during which time spermarche occurs. (19) Further masculinization, including facial hair appearance and voice change, occur during genital stage 4.

Normal variations in pubertal progression include asymmetric breast or testicular development (including a one-stage advance of unilateral development at onset) and gynecomastia (breast tissue development in boys). Pubertal gynecomastia occurs in approximately 50% of boys, begins after the onset of genital development (most often at pubic hair stage 3 to 4) and usually lasts less than 1 year. (20)

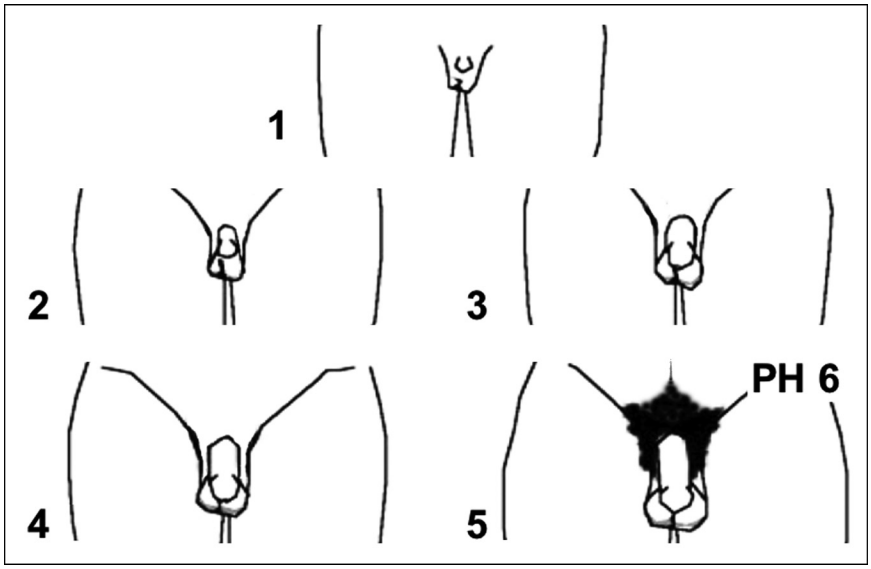

Figure 2. Genital stages in males. Stage 1 is prepubertal. Stage 2 is characterized by enlargement of the testes and scrotum but no enlargement of the penis. Stage 3 involves continued enlargement of the testes and scrotum along with penile growth, first in length and later in diameter. Stage 4 involves continued growth of the testes, scrotum, and penis, with enlargement of the glans. Stage 5 is mature male genitalia, which are shown with mature pubic hair (stage 6, PH6). Modified from Rosen DS. (2) A photographic atlas with full descriptions of pubertal stages is available from the American Academy of Pediatrics. (3)

Linear Growth in Relation to Puberty

Before puberty, growth velocity gradually decelerates slightly (Fig. 4). (11)(18) Production of sex hormones at puberty (both estrogen and testosterone) stimulates growth both directly and indirectly by augmenting growth hormone production. The pubertal growth spurt corresponds more closely to pubertal stage rather than to chronologic age per se (Fig. 4).

The pubertal growth spurt in girls begins at breast and pubic hair stage 2. Girls then typically achieve an average peak height velocity of 8.25 cm/y at approximately breast and pubic hair stage 3, about 1 year before menarche. Although linear growth slows after menarche, girls attain an average of another 7 cm thereafter, and growth is approximately 99% complete at a bone age of 15 years.

The pubertal growth spurt begins an average of 2 years later in boys than girls. Linear growth accelerates in boys beginning at genital and pubic hair stage 2. (11) Boys achieve an average peak height velocity greater than girls of 9.5 cm/y at genital and pubic hair stages 3 to 4. Growth is approximately 99% complete at a bone age of 17 years. The combination of a longer period of prepubertal growth and greater pubertal peak height velocity explains the typical height discrepancy between males and females.

Plotting growth on appropriate growth curves is important for diagnosis of growth disorders. Ordinary growth charts, which are based on cross-sectional data, are useful for identifying deviations in growth patterns that signify pathology in prepubertal children. (21) However, they provide average ranges for growth and do not reflect the shape of the growth curve during puberty, when children are entering and leaving their growth spurt at diverse ages. Therefore, longitudinal growth charts are necessary for interpreting growth after 9 years in relation to sexual maturity (Fig. 4). (11)(18) The arrest of a previously normal pubertal growth rate in an adolescent is abnormal and demands thorough evaluation for endocrine, metabolic, and systemic disorders.

Because height largely is determined genetically, a "target height" of healthy children can be crudely estimated based on parental heights, adjusting for the average differences between men and women: target height=average of the parents' heights plus 6.5 cm for boys or minus 6.5 cm for girls. Height potential is determined more accurately from bone age. (22) Because the degree of bone maturation is inversely proportional to the amount of epiphyseal cartilage growth remaining and the fraction of final height achieved at each level of bone age is known, adult height can be predicted by dividing a child's current height by this fraction. (22) For example, at a bone age of 10 years, normal girls have achieved 86.2% of adult height (boys, 78.4%), with a predictive accuracy of 1.25 in (standard deviation [SD]), whether they are 9 or 11 years old. At a bone age of 13 years, normal girls have achieved 95.8% of adult height (boys, 87.6%), with a predictive accuracy of 0.67 in (SD), whether they are 12 or 14 years old. Interpretation of bone age for height prediction purposes is performed best by a pediatric endocrinologist.

Normal Menstrual Cycle

The menstrual cycle should be considered equivalent to an examination's vital signs. (23) Because of immaturity

Table 1. Current Best Estimates for Age of Onset of Pubertal Milestones in Normal Children in the United States General Population†

Stage	Age of Onset	
	Mean	Range (5th to 95th)
Girls		
Breast Buds (B2)	10.2	8.2 to 12.1*
Pubic Hair (PH3)	11.6	9.3 to 13.9**
Menarche	12.6	11.0 to 14.1***
Boys		
Testes length 2.6 cm (4 cc) (G2)	11.5	9.5 to 13.3
Pubic Hair (PH3)	12.6	10.7 to 14.5
Testes length 3.8 cm (12 cc) (G5)	14.0	11.5 to 16.5

B2=breast stage 2, G2/5=genital stage 2/5, PH3=pubic hair stage 3
†Overweight girls' puberty is about 0.5 years earlier
*Thelarche is normal in the 7th year in non-Hispanic African American and Mexican American girls.
**Pubarche is approximtely 0.5 to 1.0 years earlier in non-Hispanic African American and Mexican American girls.
***Menarche is approximately 0.5 years earlier in non-Hispanic African American and intermediate in Mexican American girls.
Female and PH3 data are for normal-body mass index children from Rosenfield, et al.(4)
Male genital data based on Tanner and Davies. (11)

of the hypothalamic-pituitary-gonadal (HPG) axis, about 50% of menstrual cycles are anovulatory or have attenuated ovulation (24) during the first 2 years after menarche. This "physiologic adolescent anovulation" accounts for the greater menstrual irregularity and longer average intermenstrual length in the early postmenarchal years compared with adults. However, about 50% of anovulatory cycles are of normal length, so menstrual regularity is greater than ovulatory frequency would suggest. In no circumstance is the adage truer that menstrual regularity does not assure ovulatory normalcy. Although the time required for menstrual cyclicity to mature varies considerably, menstrual regularity approximates adult standards in two thirds of girls within 1 year of menarche. By 2 years after menarche, only 10% of girls have an average cycle length shorter than 21 days or longer than 45 days. By 5 years after menarche, the menstrual cycle is within the adult normal range (average cycle length, 22 to 42 days), with at least 75% of cycles being ovulatory.

The Relationship Between Puberty and Adolescent Behavior

Despite the popular concept that adolescence is inherently a period of turmoil, most teenagers do not develop significant social, emotional, or behavioral difficulties. (25) Occasional experimentation and risk-taking are normal, as are withdrawal from and conflict with parents. Adolescent behavior must be understood in the context of individual susceptibility, family upbringing and interactions, peer group interactions, changes in brain maturation, and adolescents' reaction to their perceptions of the bodily changes and to the sexual urges that are the direct consequences of puberty. Simply because a problem is displayed during adolescence does not mean that it is a direct consequence of puberty.

Many behavioral problems that emerge during adolescence have earlier roots. Although the prevalence of depression increases during puberty, many children who develop depression during adolescence have had preexisting symptoms of psychological distress. Similarly, most delinquent teenagers have had antecedent problems at home and school.

Girls who mature early in Western cultures are more popular. However, they have more emotional problems; lower self-image; and higher rates of depression, anxiety, and disordered eating than their peers. Early maturation appears to be a particular risk factor for problem behavior among girls who have had a history of difficulties before adolescence, when they have more opposite-sex friendships and relationships, and when they attend coeducational schools. Early maturing boys also are more popular, but they are at higher risk for engaging in antisocial and aggressive behaviors and precocious sexual activity, particularly when they forge friendships with older peers.

Short-term administration of testosterone or estrogen has minimal effects on behavior or mood in adolescents. (26)(27) Thus, variation in hormone concentrations accounts for only a small fraction of adolescents' affective issues; social influences account for considerably more. Although there is little evidence that psychological difficulties stem directly from hormonal changes during normal puberty, it is likely that the bodily changes of adolescence play a role in the development of a negative body image when they occur out of synchrony with sociocultural norms.

Problems with initiating and maintaining sleep are common in adolescents and contribute a small amount to poor school performance. (28) Insufficient sleep might be due to environmental factors (eg, social and

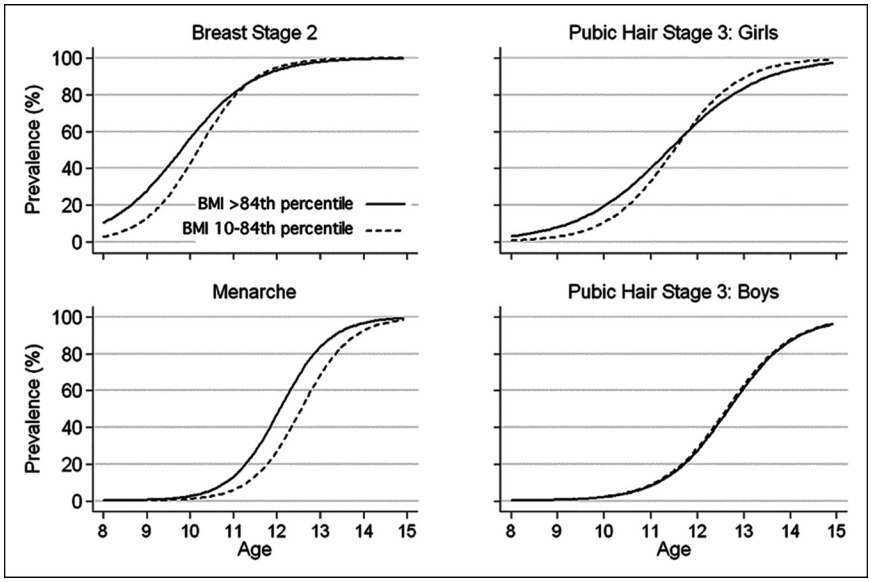

Figure 3. Relationship of body mass index (BMI) status to the prevalence of pubertal milestones. Stage 2 breast development differs significantly according to BMI status from ages 8.0 through 9.6 years. Similarly, pubarche in girls differs significantly by BMI status from ages 8.0 through 10.2 years. Menarche differs significantly by BMI status from ages 10.6 through 12.9 years. There was no evidence of an association between excess adiposity and pubarche in boys. Modified from Rosenfield et al. (4)

academic pressures), but intrinsic factors clearly play an important role. A 50% decline in the intensity of deep (slow wave, delta) sleep occurs during adolescence, and 50% of this change occurs between 12 and 14 years of age. (29) Recent evidence indicates that this change is related to age and sex, beginning earlier in girls, but not to pubertal stage. It has been proposed that this shift is a manifestation of the widespread synaptic pruning that is related to the emergence of adult cognitive capacity.

The causal direction of the link between pubertal development and the quality of family relationships has come into question. Several studies have indicated that family dynamics may affect the timing and course of puberty, with earlier and faster maturation observed among adolescents raised in homes characterized by more conflict and among girls from homes in which the biologic father is not present.

Effects of Puberty on Other Body Systems

In addition to the classic pubertal changes, the sex steroid changes of puberty bring about physiologic alterations in a wide variety of systems. In both sexes, the hemoglobin concentration increases slightly from an average of 12.5 g/dL (125 g/L) in 2 to 6 year olds to an average of 13.5 g/dL (135 g/L) during late childhood and early puberty. The red blood cell mass increases further when the growth spurt begins, with adult males ultimately attaining hemoglobin values slightly higher (range, 13.5 to 17.5 g/dL [135 to 175 g/L]) than those of females (12.0 to 15.5 g/dL [120 to 155 g/L]), which remain nearly at mid-childhood values. (30) The total alkaline phosphatase concentration elevates transiently to as high as 525 U/L (8.8 μkat/L) (girls) and 585 U/L (9.8 μkat/L) (boys), reflecting the high osteoblastic activity of rapid bone growth. (30) Bone-specific alkaline phosphatase peaks at pubertal stage 3 in both girls (average, 80 μg/L) and boys (100 μg/L). (31) Total cholesterol peaks in early puberty; low-density lipoprotein cholesterol peaks in later puberty. (32) High-density lipoprotein cholesterol concentrations remain relatively constant, although boys have a slight decrease from early to mid-puberty. Triglycerides tend to rise slightly. Blood pressure gradually increases. (33) It is important to assess blood pressure in relation to sex-specific, height- and age-matched normal values, using the 95th percentile as a criterion for separating normal from those who require evaluation (Table 2). Serum concentrations of renin and aldosterone decrease considerably and those of thyroid hormones, calcium, and phosphate all decrease slightly throughout childhood to reach adult values when puberty is complete.

Recognizing Disorders of Puberty

Pubertal disorders can be recognized when puberty (or menses) is too early, too much, too late, or too little. Although it is beyond the scope of this review to deal comprehensively with disorders of puberty, the general principles involved in recognizing and differentiating these conditions from normal are discussed.

Puberty Too Early: Premature (Precocious) Puberty

Thelarche or pubarche before 8.0 years of age in girls and pubarche or genital development before 9.0 years in boys is considered to be premature, (12) except in the case of

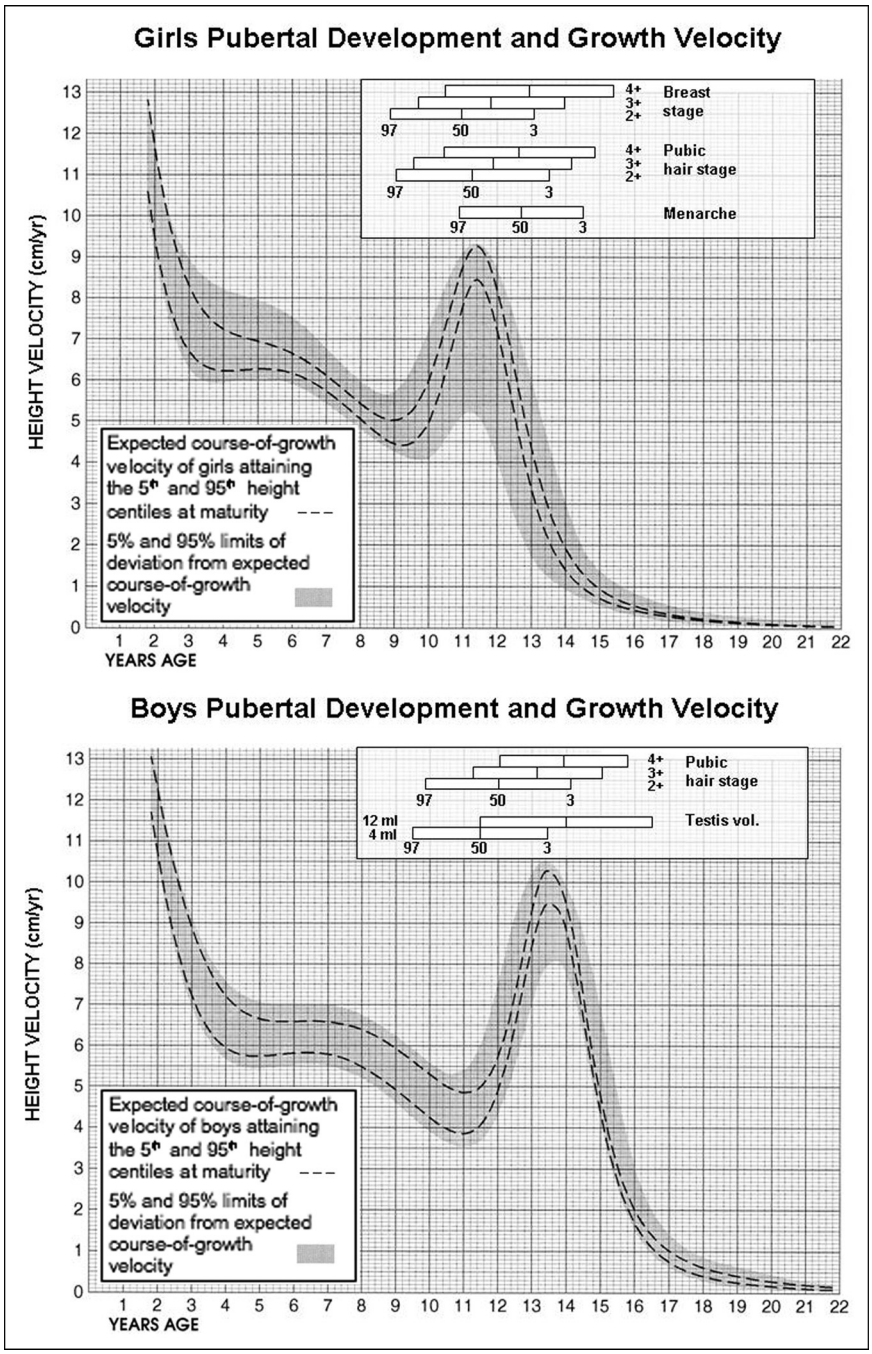

Figure 4. Relationship of key pubertal stages to pubertal growth velocity. Top panel: After a slight deceleration in growth, female puberty begins with breast development. Pubic hair development soon follows, and linear growth accelerates. Girls achieve peak height velocity approximately 1 year before menarche. Note that the current estimates for attainment of pubertal milestones in normal-weight girls (Table 1) are about 0.25 years (pubic hair stage 3) to 0.5 years (breast stage 2) earlier than these 1985 estimates from Tanner and Davies (1985). (11) Bottom panel: After a slight deceleration in growth, male puberty begins with testicular enlargement to genital stage 2 (volume >3 mL). Pubic hair development soon follows, and linear growth accelerates. Boys achieve peak height velocity before entering genital stage 5 (testis volume 12 mL). Note that the current estimates for pubic hair stage 3 milestones (Table 1) are 0.5 year earlier than these 1985 estimates. Modified from Bock and Rosenfield (18) and Tanner and Davies. (11)

Table 2. 95th Percentile of Blood Pressure (BP) for Girls and Boys Ages 1 to 17 Years by Percentiles of Height

	95th Percentile Systolic BP (mm Hg)			95th Percentile Diastolic BP (mm Hg)		
Height Percentile:	5%	50%	95%	5%	50%	95%
Girls						
Age (yr)						
1	101	104	107	57	58	60
3	104	107	110	65	66	68
5	107	110	113	69	71	73
7	110	113	116	73	74	76
9	114	117	120	75	77	79
11	118	121	124	78	79	81
13	121	125	128	80	82	84
15	124	128	131	82	83	86
17	126	129	132	83	84	86
Boys						
Age (yr)						
1	98	102	106	55	57	59
3	104	109	113	63	65	67
5	108	112	116	69	71	74
7	110	115	119	74	76	78
9	113	117	121	76	79	81
11	116	121	125	78	80	83
13	121	126	130	79	82	84
15	127	131	135	81	83	86
17	132	136	140	85	87	89

Data from Horan. (33)

non-Hispanic African American and Mexican American girls, in whom thelarche is normal in the seventh year (Table 1). A clinically significant excess of sex hormone output is suggested if puberty advances rapidly or is accompanied by a growth spurt. Sexually precocious children are at risk for the premature epiphyseal fusion that leads to the paradox of short adult stature despite tall stature in childhood.

Most sexual precocity does not have a serious cause that needs to be treated. Two extreme variants of normal are common, particularly in girls, in whom they account for more than 15% of office visits (34): idiopathic premature thelarche and idiopathic premature pubarche/adrenarche.

Idiopathic premature thelarche may begin unilaterally or bilaterally. This change occurs in isolation; affected girls do not have pubic hair development or a pubertal growth spurt. The breast development may regress after a few months or it may persist in proportion to somatic growth until normal true puberty begins at a normal age. Premature thelarche usually is due to minimal activation of the hypothalamic-pituitary-ovarian axis with predominant FSH secretion, (35)(36)(37) but estrogen formation in excess adipose tissue and exogenous estrogen exposure, such as from topical tea tree oil, should be considered.

Premature thelarche occasionally is the first sign of progressive true sexual precocity, indicating the need for close observation of pubertal development, height velocity, and bone age. Breast development in a boy before puberty (that is, unaccompanied by pubertal genital and pubic hair development) is abnormal, and a feminizing disorder such as a neoplasm must be ruled out.

Premature pubarche is characterized by slowly progressive pubic or axillary hair development and may be accompanied by increased body odor or mild acne. This development is not accompanied by breast or testicular enlargement or a pubertal growth spurt. Premature pubarche may be idiopathic, due to apparent sexual hair follicle hypersensitivity to the normal traces of androgen of early adrenarche, or due to premature adrenarche or anabolic steroid exposure. Premature adrenarche ordinarily is diagnosed when premature pubarche is accompanied by a mild elevation of plasma dehydroepiandrosterone sulfate (DHEAS), typically to 40 to 130 μg/dL (1.1 to 3.5 μmol/L), which is above the upper limit for normal preadrenarchal children and in the range for normal early pubertal children. (38) The DHEAS elevation seems to be caused usually by early maturation of the zona reticularis of the adrenal cortex. Premature adrenarche occasionally may be a precursor of polycystic ovary syndrome (PCOS) or, rarely, may be the first evidence of a virilizing disorder. Close observation of pubertal development, height velocity, and bone age is indicated.

Complete precocious puberty results from early activation of the HPG axis, with gonadotropins stimulating

sex hormone production. The condition is five times more common in girls than in boys, and 90% of cases in girls are idiopathic. Conversely, complete precocious puberty is idiopathic in only 50% of boys. Consequently, organic central nervous system disorders, of virtually any cause, are more prevalent in precocious boys than in precocious girls. An activating mutation of *GPR54*, a key factor in the hypothalamic signaling system regulating pubertal GnRH release, has been reported to cause premature puberty. (39)

Precocity in the 6- to 8-year age range usually is not rapidly progressive and may not require specific treatment. Overweight and obesity may be the underlying cause in many such cases. However, rapidly progressive precocity, particularly if before 6 years of age or if associated with vaginal bleeding at breast stage 2, requires investigation and treatment.

Other causes of precocious puberty include gonadotropin-independent precocious puberty, which results from intrinsic adrenal or gonadal disorders or exogenous hormones. The most common of these conditions are nonclassic congenital adrenal hyperplasia (which is mildly virilizing), McCune-Albright syndrome (which typically feminizes girls), and "testotoxicosis" (primary Leydig cell hyperplasia, which causes moderate masculinization in boys); neoplasms are rare possibilities to consider.

Vaginal bleeding in the absence of breast development is not likely to be hormonally mediated. Alternate causes, such as foreign body, abuse, or genital tract neoplasm, should be explored.

Puberty Too Much: Sex Steroid Excess Disorders

Hirsutism, excessive sexual hair development in a female (as distinguished from a generalized excess of body hair or hypertrichosis), is a normal variant when mild and isolated. However, when accompanied by menstrual abnormality or when severe, hyperandrogenism must be considered, and PCOS accounts for about 85% of these cases. (40) PCOS is a disorder of otherwise unexplained hyperandrogenic anovulation that manifests typically in the perimenarchal stage of development. PCOS generally is due to functional ovarian hyperandrogenism. About 50% of affected girls are obese, and 50% of these have metabolic syndrome.

During puberty, most boys develop transient gynecomastia. However, a mid-adolescent female degree of breast development in a boy ("macromastia") can be expected to persist. Although usually an extreme variant of normal, this degree of breast development is an indication for an evaluation to rule out estrogen excess, androgen deficiency, or liver dysfunction.

Puberty Too Late: Delayed Puberty

Delayed puberty is defined as lack of breast development by age 13.0 years in girls and lack of pubertal testicular development (genital stage 2) by age 14.0 years in boys (Table 1). The delay is accompanied by slowing of linear growth velocity, and sometimes the accompanying short stature is the primary complaint.

Most delayed puberty does not have a serious cause because it is due to an extreme variant of normal, known as constitutional delay of pubertal growth and development, which is seen more commonly in boys. This condition results from unexplained delay in the onset of pubertal HPG activation, ie, prolongation of the physiologic gonadotropin deficiency of childhood. Once puberty begins, its course and tempo are normal, and catch-up growth to target height occurs. If puberty does not begin in a boy by 18 years of age, it is pathologic. In the meantime, the self-image of many constitutionally delayed boys benefits significantly from short physiologic (low-dose) courses of androgen replacement therapy under the care of a pediatric endocrinologist.

Delayed puberty also can be caused by a variety of chronic endocrine, metabolic, and systemic disorders. Undernutrition underlies the delayed puberty of disadvantaged populations. Screening tests for general health (eg, complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate, and thyroid function tests) are indicated, as are gonadotropin concentrations to assess the possibility of hypogonadism.

Puberty Too Little: Hypogonadism

Hypogonadism is suspected when the patient experiences too little pubertal development, micropenis, or cryptorchidism. Obesity is a common confounder in the diagnosis of micropenis because a prominent suprapubic fat pad obscures penile development ("pseudomicropenis"), but normalcy of penile development is demonstrable by palpation of the full length of the penile corpus. Failure of the testes to descend is a risk factor for infertility and testicular malignancy. (41) These risks appear to increase with the severity of the cryptorchidism and time to orchiopexy beyond infancy. Retractile testes were believed to be spared these risks, but recent studies suggest that about one third of retractile testes ascend to become cryptorchid and lose germ cells. Accordingly, health supervision visits should include assurance of the scrotal position of the testes.

Primary hypogonadism is hypergonadotropic, with FSH, in particular, being elevated. Secondary (pituitary) or tertiary (hypothalamic) hypogonadism is indicated by absolutely or inappropriately low luteinizing hormone values. The bone age is important in determining whether gonadotropin concentrations are appropriate. Because neuroendocrine puberty may not begin until the bone age reaches a pubertal level, prepubertal gonadotropin values do not necessarily rule out primary hypogonadism before this stage of bone age. After a pubertal bone age is achieved, prepubertal gonadotropin concentrations rule out primary hypogonadism.

At the other extreme, after 18.0 years of age, hypogonadotropic hypogonadism is indicated by lack of elevated gonadotropin values, not necessarily by low values. In between, it may be difficult to differentiate constitutionally delayed puberty from hypogonadotropic hypogonadism unless there are clues to specific conditions.

The age of onset and severity determine the manifestations of hypogonadism. Congenital hypogonadism may cause disorders of sexual differentiation in genetic males. Complete hypogonadism that is present prepubertally causes sexual infantilism in both sexes, and puberty will never occur. Less severe hypogonadism or hypogonadism that manifests in the early teenage years slows or arrests the pubertal progression.

In cases of untreated severe hypogonadism, epiphyseal closure is delayed, resulting in taller stature than would be expected from the family target height. Hypogonadism after complete puberty has been attained causes menstrual disturbance in females and impotence and gynecomastia in males.

Primary (hypergonadotropic) hypogonadism usually is due to the gonadal dysgenesis that results from sex chromosomal errors in cell division. In girls, the common cause is Turner syndrome, which is due to a deficiency of genes on the X chromosome. Short stature typically is present from early childhood. Many affected girls otherwise lack the Turner phenotype, which includes webbed neck, cubitus valgus, and other typical features. In boys, the common cause is Klinefelter syndrome, which is due to an extra X chromosome. The testes are inappropriately small for the degree of masculinization, and affected boys often have a history of learning disabilities.

Gonadotropin deficiency may be due to molecular defects in HPG signaling pathways, such as in the kisspeptin-GPR54 system. The deficiency may be either congenital (which should be suspected if anosmia or midline craniofacial defects are associated) or acquired (which commonly is a consequence of undernutrition, tumor, trauma, or autoimmune disease). Gonadotropin deficiency should also be suspected if there are other pituitary hormone deficiencies.

Girls are particularly vulnerable to the reproductive effects of undernutrition and stress. Anorexia nervosa is the prototypic form of eating disorders and is a common cause of hypogonadotropism in teenagers. This syndrome of undernutrition is due to voluntary starvation associated with a particular psychological dysfunction that results in amenorrhea. (42) Experimentally, the gonadotropin deficiency has been corrected by opioid antagonists.

The weight changes leading to cessation or restoration of menstrual cycles are in the range of 10% to 15% of body weight. Recovery of menses is associated with attainment of sufficient mental health to achieve a critical amount of body fat, which typically entails reaching a body mass index (BMI) within the normal range.

Athletic amenorrhea is a related disorder that refers to the hypothalamic anovulation resulting from the low body fat stores associated with excessive exercise and obsession with weight control. The female athletic triad consists of menstrual disturbance, eating disorder, and osteoporosis. (1) Primary or secondary amenorrhea, oligomenorrhea, or excessively frequent periods due to luteal insufficiency are common. The BMI does not accurately reflect body fat stores in athletes, which is the critical factor related to the menstrual disorders. Leptin concentrations are decreased significantly and are a major contributor to the gonadotropin deficiency. (43)

Menstrual Disorders

Although menstrual irregularities are common in adolescents, they are too often mistakenly disregarded. (23) Any disorder that can affect female puberty can cause the following types of menstrual dysfunction: *primary amenorrhea* (failure of menses to begin by 15.0 years of age or within 3 years of thelarche), *secondary amenorrhea* (cessation of menstrual periods for 90 days or more after initially menstruating), *oligomenorrhea* or *amenorrhea* (infrequent periods or no periods within any year after initially menstruating), or *dysfunctional uterine bleeding* (anovulatory bleeding that is excessive in amount or frequency). Even within the first year after menarche, evaluation should be considered for an unusual degree of menstrual irregularity, such as missing a period for 90 days for even one cycle, bleeding more often than at 21-day intervals, or bleeding for more than 7 days or requiring pad or tampon changes more than every 1 to 2 hours. By 2 postmenarchal years, failure to establish or

sustain menstrual cyclicity that is normal by adult standards carries about a two-thirds risk of persistent oligo-ovulation. (44) Thus, failure to establish normal adult cyclicity by this time is a strong indication for investigation.

Pregnancy is always the first consideration. Most menstrual disorders are due to anovulatory disorders; PCOS, nutritional disturbance, and hyperprolactinemia are the most common conditions. Prolactin excess is accompanied by galactorrhea in about 50% of cases and may cause a hypogonadotropic or a hyperandrogenic picture. Unique causes to consider in the differential diagnosis of dysfunctional uterine bleeding are sexual abuse, genital tract or feminizing neoplasm, and bleeding diathesis. Unique causes to consider in the case of primary amenorrhea are delayed puberty, aplasia of the genital tract, and disorders of sex development. Inspection of the external genitalia, which is recommended as part of the routine annual comprehensive physical examination of children and adolescents at all ages, is likely to detect the latter conditions; an internal pelvic examination seldom is necessary for diagnosis. (45) Nevertheless, normal external genitalia do not exclude a disorder of sex development. Complete androgen insensitivity presents as a well-developed normal female who has primary amenorrhea and scanty pubic hair, often associated with an inguinal hernia, and whose evaluation reveals her to be a genetic male with cryptorchid testes and male testosterone concentrations.

Summary

All of the following are based on strong research evidence:

- Breast development before 8.0 years of age is unusual in the general population of normal-weight girls in the United States, but breast development is normal in the seventh year in girls of minority ethnic status (non-Hispanic African American and Mexican American).
- Obesity advances the onset of puberty in girls.
- Pubertal development in boys is 1 to 2 years later than in girls, on average.
- Missing a menstrual period for 90 or more days or having an average cycle length less than 21 days is abnormal for a girl of any age, and an average cycle length of more than 45 days by 2 years after menarche is a risk factor for ongoing oligo-anovulation.
- Pubertal growth and development and menstrual cyclicity are sensitive indicators of general health.

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PIR Quiz

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6. Normal pubertal development varies according to a child's weight and ethnicity. Which of the following clinical findings indicates premature pubertal development?

   A. Penile enlargement in a 10-year-old African American male of normal weight.
   B. Stage 3 pubic hair in a 7-year-old Mexican American girl of normal weight.
   C. Testicular enlargement in a 9-year-old white boy who is obese.
   D. Thelarche in a 7-year-old African American girl of normal weight.
   E. Thelarche in a 9-year-old white girl who is obese.

7. You are seeing a 13-year-old girl who experienced menarche 3 months ago. Her physical examination shows that the areolae form a secondary mound above the contour of her breasts. Her pubic hair is curly and coarse and covers the lower portion of her mons pubis. Which of the following is the *most* accurate description of her Sexual Maturity Rating?

   A. Breast: stage 2, pubic hair: stage 3.
   B. Breast: stage 3, pubic hair: stage 3.
   C. Breast: stage 3, pubic hair: stage 4.
   D. Breast: stage 4, pubic hair: stage 4.
   E. Breast: stage 4, pubic hair: stage 5.

8. Which of the following is a true statement regarding normal pubertal development?

   A. Behavioral changes in adolescence are a direct manifestation of increases in sex hormone concentrations.
   B. Bone age is an accurate determinant of height potential in boys and girls.
   C. Most girls miss periods for 90 days within 1 year of menarche.
   D. Pubertal gynecomastia is rare and should prompt an investigation.
   E. The pubertal growth spurt in girls typically occurs within 2 to 3 months after menarche.

9. Which of the following patients should undergo an evaluation to rule out organic pathology as a cause for abnormal pubertal development at this time?

   A. A 6-year-old white girl who has unilateral thelarche, normal growth velocity, and no pubic hair development.
   B. A 7-year-old Mexican American boy who has breast development and testicular enlargement.
   C. A 13-year-old African American girl who has a recent growth spurt and no menarche.
   D. A 13-year-old white boy who has no testicular enlargement and normal growth velocity.
   E. A 16-year-old African American girl who has excessive pubic hair and normal menstrual cycles.

HealthyChildren.org Parent Resources from AAP

The reader is likely to find material to share with parents that is relevant to this article by visiting this link: http://www.healthychildren.org/English/ages-stages/gradeschool/puberty/pages/default.aspx.

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