Pubertal Development

Risa M. Wolf, MD,* Dominique Long, MD*

*The Division of Pediatric Endocrinology, Johns Hopkins Hospital, Baltimore, MD.

EDITOR'S NOTE

Readers will immediately notice that what most of us recognize as "Tanner Staging" has been replaced by the term "Sexual Maturity Rating." A quick review of recent literature will show that "Sexual Maturity Rating" is becoming the more accepted term.

Educational Gap

Puberty is a time of rapid linear growth and multiple physical changes. Accurately identifying the onset of puberty and how this relates to height velocity is essential to recognizing normal and abnormal growth patterns. The onset of puberty is also a critical time for the identification and treatment of individuals with persistent gender dysphoria.

Objectives   After completing this article, the reader should be able to:

1. Describe the usual sequence and timing of male and female pubertal development.

2. Understand the physiologic factors that contribute to the onset of puberty.

3. Distinguish normal from abnormal puberty and when to undertake further evaluation.

4. Understand the relationship between puberty and linear growth.

5. Describe the factors that affect the timing of puberty.

DEFINITION

Puberty is broadly defined as the time at which a child develops secondary sexual characteristics and reproductive function. Puberty results from a complex sequence of biological events mediated by genetic, hormonal, and environmental factors that are characterized by the maturation of gametogenesis and secretion of gonadal hormones. Adolescence is a term often used interchangeably with puberty and is a stage that encompasses puberty as well as cognitive, psychological, and social changes.

Gonadarche refers to sex hormone production from the ovary or testis and is triggered by luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion from the pituitary. Adrenarche represents the increase in adrenal

androgen production that leads to the development of pubic hair (pubarche), axillary hair, sebaceous gland (acne), and apocrine gland (sweating, body odor). Thelarche is the onset of breast development with the development of breast buds. Menarche is the onset of menstrual cycles in females.

PHYSIOLOGY

Pubertal development requires activation of the hypothalamic-pituitary-gonadal (HPG) axis. The hypothalamus secretes pulsatile gonadotropin-releasing hormone (GnRH), which signals the gonadotroph cells in the anterior pituitary to release the gonadotropins LH and FSH. In general, LH primarily stimulates specialized interstitial cells (theca cells in the ovary or Leydig cells in the testes) to produce androgen, while FSH primarily stimulates the ovarian follicle or seminiferous tubules to produce estradiol, inhibin, and gametes (egg or sperm). Interstitial and follicular/tubular compartments also act through paracrine mechanisms (communication of cell to surrounding cells) to form estradiol and regulate sex steroid and gamete development.

In girls, FSH promotes the growth of ovarian follicles and, together with LH, signals the ovary to make estradiol. Estradiol production results in breast development and growth of the skeleton. As estradiol promotes maturation of the skeleton, eventually estradiol also leads to fusion of the growth plates and cessation of growth. At the time of menarche, estradiol prepares the endometrium of the uterus for implantation.

In boys, LH stimulates the Leydig cells of the testes to produce testosterone that, in turn, promotes growth of the seminiferous tubules, resulting in an increase in testicular volume. Testosterone production due to FSH also induces growth of the penis, deepening of the voice, growth of hair, and increased muscularity.

Sex steroids provide negative feedback on GnRH and gonadotropin production. Inhibin is a hormone secreted by the gonads that also provides negative feedback by decreasing FSH production. Later in development, ovulation in girls results from maintenance of a high estradiol concentration for a critical amount of time; this estradiol concentration provides positive feedback, which causes the LH surge that results in ovulation.

Pediatric assays should be used when assessing gonadotropin and sex hormone concentrations in children, as may be necessary in the evaluation of ambiguous genitalia or precocious puberty. LH and FSH concentrations are high during the first 3 postnatal months. LH decreases to almost undetectable values by the age of 6 months in boys and girls. FSH concentrations also decrease after 6 months but can remain elevated in girls until age 3 to 4 years. The HPG axis then remains quiescent until puberty.

LH values vary widely during childhood, ranging from 0.06 to 4.77 mIU/mL (0.06–4.77 IU/L) in boys and 0.1 to 14.7 mIU/mL (0.1–14.7 IU/L) in girls. Generally, LH is the most useful gonadotropin to assess for the onset of puberty. An LH value of greater than 0.3 mIU/mL (0.3 IU/L) is consistent with the onset of central puberty. However, an undetectable basal LH value alone has low sensitivity for central puberty. Pubertal FSH concentrations range from 0.21 to 8.74 mIU/mL (0.21–8.74 IU/L) in boys and 0.64 to 10.98 mIU/mL (0.64–10.98 IU/L) in girls. Importantly, FSH concentrations have been noted to be elevated in premature thelarche, a normal variant consisting of breast development not associated with central precocious puberty. An elevated FSH value, therefore, is not a reliable measure of the onset of central puberty.

Estradiol is the primary circulating estrogen in girls, and ultrasensitive assays using liquid chromatography/tandem mass spectrometry (LC/MS/MS) technology are most useful when measuring concentrations in prepubertal girls. Estradiol values are generally equal to or less than 16 pg/mL (58.7 pmol/L) in prepubertal girls. By age 10 to 11 years, estradiol values are equal to or less than 65 pg/mL (238.6 pmol/L), by age 12 to 14 years are equal to or less than 142 pg/mL (521.3 pmol/L), and by age 15 to 17 years are equal to or less than 283 pg/mL (1038.9 pmol/L). Estradiol concentrations in boys are usually less than 31 pg/mL (113.8 pmol/L).

Testosterone levels by LC/MS/MS in prepubertal girls are equal to or less than 8 ng/dL (0.3 nmol/L) and remain less than 33 ng/dL (1.2 nmol/L) by Sexual Maturity Rating (SMR) 5. Testosterone levels in boys at SMR 1 are generally less than 5 ng/dL (0.2 nmol/L), less than 167 ng/dL (5.8 nmol/L) at SMR 2, between 21 and 719 ng/dL (0.7–25 nmol/L) at SMR 3, 25 to 912 ng/dL (0.9–31.7 nmol/L) at SMR 4, and 110 to 975 ng/dL (3.8–33.8 nmol/L) at SMR 5.

Pulsatile GnRH release and consequent pulsatile LH and FSH secretion occurs before most physical signs of puberty. In early puberty, this pulsatile release takes place mostly at night, but as puberty progresses, gonadotropin release develops into the established adult pulsatile pattern throughout the day. This "pulse generator" appears to be fully intact at birth and is likely inhibited by unknown factors during childhood.

The initiation of pulsatile GnRH release is not completely understood, although indirect upstream signaling pathways have been found to regulate GnRH-secreting neurons, such as kisspeptin, leptin, and gonadal steroids. Kisspeptins are peptide products of the *KiSS-1* gene and are the natural ligands for the G protein-coupled receptor GPR54, which

is found on GnRH neurons. Kisspeptins stimulate GnRH neurons to secrete GnRH. Interestingly, kisspeptin receptor and ligand have also been found within the brainstem, spinal cord, pituitary, ovary, prostate, and placenta, suggesting regulation of the reproductive axis on multiple levels. The role of kisspeptins as stimulators of GnRH secretion became apparent when mutations in the kisspeptin receptor were found to be associated with idiopathic hypogonadotropic hypogonadism, while activating mutations have been associated with precocious puberty. Kisspeptin is a target for steroid hormones and may explain how sex steroids exert positive and negative feedback on GnRH secretion. (1)

Leptin is a peptide produced by adipose tissue that circulates in proportion to energy stores. It provides negative feedback in the hypothalamus to control appetite and energy use. Although leptin does not have a direct role in puberty induction, studies have demonstrated that leptin targets the KiSS1 neurons and likely influences GnRH secretion. (1)

CLINICAL ASPECTS OF PUBERTY

Although puberty often occurs in a predictable pattern, the age of onset, sequence, and tempo may vary. SMR staging of sexual development or Tanner staging provides a consistent method of monitoring a child's progression through puberty. Separate scales are used for gonadarche (breasts in females and testicular size in males) and pubic hair (Table 1).

Accurate staging for breast and testicular development requires palpation. Breast tissue cannot be distinguished from adipose tissue by inspection, and inspection alone can lead to inaccurate pubertal staging. Palpation of a subareolar breast bud indicates the onset of puberty in girls. Direct measurement of testicular size by palpation is preferable to visual estimation. A testicular volume of 3.0 mL or a length of equal to or greater than 2.5 cm indicates SMR 2 gonadarche. Pubic hair development may result from gonadal or adrenal androgen production. In some cases, distinguishing increased body hair from early sexual hair growth can be difficult. Generally, pubic hair is coarse and curly, while body hair is fine and straight.

FEMALE PUBERTAL DEVELOPMENT

Girls normally begin puberty between 8 and 13 years of age. (2) The initial physical sign of puberty is most often thelarche. Ovarian enlargement and growth acceleration are present at the onset of breast development but may not be obvious at initial presentation. Thelarche is typically followed by pubarche, although 15% of girls have pubarche as the first sign of puberty. Recently, Biro et al (3) examined

TABLE 1. **Sexual Maturity Rating in Boys and Girls**

BREAST DEVELOPMENT	
Prepubertal	No breast buds
Stage 2	Subareolar breast bud
Stage 3	Elevation of the breast contour and enlargement of the areola
Stage 4	Areola forms a secondary mound above the contour of the breast
Stage 5	Mature female breast with dependent breast contour, recession of areola
PUBIC HAIR DEVELOPMENT	
Prepubertal	Prepubertal, may be some vellus hair
Stage 2	Sparse, fine, straight pubic hairs, typically at base of penis or along labia
Stage 3	Long, dark, curly pubic hairs limited to mons pubis
Stage 4	Pubic hair is adult in quality, not yet spread to thighs
Stage 5	Pubic hair has distribution of inverted triangle with spread to thighs
	In boys, there is a stage 6 for pubic hair when pubic hair rises up the midline
TESTICULAR/PENILE DEVELOPMENT	
Prepubertal	Prepubertal
Stage 2	Enlargement of the testes and scrotum, no enlargement of penis
Stage 3	Enlargement of testes and scrotum, penis grows in length
Stage 4	Further enlargement of the testes and scrotum, penis grows in length and diameter
Stage 5	Mature male genitalia

hormonal changes in peripubertal girls and found dehydroepiandrosterone sulfate (DHEA-S) concentrations increased 24 months before breast development, while estradiol and testosterone increased between 6 and 12 months before breast development. In a separate study, the same research group also found the onset of breast development to occur at 8.8, 9.3, 9.7, and 9.7 years for African American (AA), Hispanic, white non-Hispanic (NHW), and Asian participants, respectively. (4) Breast development may occur up to 1 year earlier in AA and Mexican American girls and can be normal in the 7th year in these specific populations.

Breast development may be asymmetric and can be associated with breast tenderness. Although asymmetry of the breasts is common between SMR 2 and 4, other causes of

asymmetry include juvenile fibroadenoma or abscess. Sixty-eight percent of breast masses in adolescents are due to fibroadenomas, which are more common in AA girls. Fibroadenomas are not associated with malignancies and are usually 2 to 3 cm, although giant fibroadenomas are greater than 5 cm. The peak incidence occurs in late adolescence. Less common causes of breast masses in adolescent girls include duct obstruction, retroareolar cysts, phyllodes tumors, intraductal papilloma, juvenile papillomatosis, breast contusion, and cancer. Breast cancer is extremely rare in girls younger than age 14 years. The cause of an adolescent breast mass can often be determined by history and serial physical examinations. Imaging may be helpful in some cases, most often ultrasonography, and if indicated, biopsy. (5)

Gonadarche and adrenarche are frequently temporally related but are distinct processes. Although corticotropin production is required for adrenarche, the trigger for adrenarche is not fully understood. The typical sequence of pubertal events is shown in Figure 1. Rosenfield et al (6), using data from National Health and Nutrition Examination Survey (NHANES)-3, found the mean onset of SMR 3 pubic hair in nonobese girls to be 11.57 years, 11.6 years in NHW, 10.65 years in non-Hispanic black, and 11.63 years in Mexican American girls. This compared to an earlier mean onset of SMR 3 pubic hair of 11.39 years in obese girls.

Menarche refers to the first menstrual bleed and usually occurs 2 to 2.5 years after the onset of puberty. Physiologic leukorrhea due to estradiol stimulation of the vaginal mucosa typically begins 6 to 12 months before menarche and results in a thin, white vaginal discharge with no odor. Initially, menarche is often not associated with ovulation. The timing of menarche has not been shown to be advancing as quickly as other pubertal changes, with the average age of menarche between 12 and 12.5 years, similar to that reported in the 1970s. Examining the NHANES-3 database, the Rosenfield group found the mean age of menarche in obese girls was 12.06 years compared to 12.57 in nonobese girls. (6)

MALE PUBERTAL DEVELOPMENT

Boys typically begin puberty between ages 9 and 14 years. The onset of male puberty is marked by testicular enlargement, and usually within 6 months, penile length increases

Typical Sequence of Pubertal Events in Males

G2 → G3 → PH2 → G4 → PH 3 → PHV → PH4 → G5 → PH5

Typical Sequence of Pubertal Events in Females

B2 → PH2 → PHV → B3 → PH3 → PH4 → B4 → Menarche → PH5 → B5

Figure 1. Sequence of pubertal events. B=breasts, G=gonadarche, PH=pubic hair, PHV=peak height velocity.

and pubic hair develops. Testicular enlargement at the onset of puberty is described as a volume greater than 3 mL or testicular length equal to or greater than 2.5 cm. Pubarche follows, with the development of pubic hair and other secondary sexual characteristics, including axillary hair, body odor, and sometimes acne. Within 1 to 1.5 years of starting puberty, boys have often reached SMR 3 for pubic hair. Linear growth begins to accelerate during genital and pubic hair SMR 2, and the pubertal growth spurt and spermarche typically occur between SMR 3 and 4 or around a testicular volume of 10 to 12 mL (Fig. 1). (7) Spermarche is the term used for the time of the first sperm production and is due to the production of testosterone. Further masculinization, with facial hair appearing and voice deepening, typically occurs in the fourth stage of puberty. Although adrenarche and gonadarche frequently overlap, adrenarche can sometimes precede gonadarche by 1 to 2 years in boys.

At the onset of puberty, there can be asymmetric testicular development and gynecomastia. Pubertal gynecomastia occurs in approximately 50% of boys, usually in pubic hair SMR 3 to 4, and typically resolves within 2 years. Gynecomastia that persists or prepubertal breast development in a boy should prompt further evaluation for estrogen excess, androgen deficiency, or liver dysfunction.

Historically, the mean onset of puberty in boys was reported to be around 11.64 (SD 1.07) years, with 95% of boys experiencing the onset of genital development between 9.5 and 13.5 years. (8)(9) More recently, the actual onset of male puberty has been shown to be earlier than it was 40 years ago, and there are differences by ethnicity. Data from the Pediatric Research in Office Settings (PROS) Network published in 2012 showed that the mean age of pubertal onset in boys was 6 months to 2 years earlier than in past studies, with mean age of onset of SMR 2 gonadarche for NHW, AA, and Hispanic boys of 10.14, 9.14, and 10.04 years, respectively, and for SMR 2 pubic hair of 11.47, 10.25, and 11.43 years, respectively. (10) PROS data concluded that overall, AA boys start puberty earlier, but the transition to SMR 5 puberty at age 15 years was similar for all boys, regardless of ethnicity.

The testicular self-examination should be initiated during the pubertal years. Such examination can help identify any testicular abnormalities, particularly testicular masses. Testicular cancer is the most common malignancy in men ages 20 to 35 years, and routine self-examination has been shown to help with early diagnosis and treatment that improves outcomes.

GROWTH IN PUBERTY

Growth velocity is important to monitor in all children, especially during puberty, because normal and abnormal variants

of pubertal maturation may come to medical attention due to departure from the child's established growth pattern. Further, systemic illnesses may first present with poor growth before the onset of other symptoms, as is often the case in inflammatory bowel disease (IBD) or celiac disease. Of note, girls have their growth spurt earlier, typically between SMR 2 and 3, while boys have their growth spurt between SMR 3 and 4 (Fig. 1). (11) The pubertal growth spurt occurs over 2 to 3 years, with peak height velocity (HV) in boys ranging from 5 to 11 cm/year and in girls from 6 to 10 cm/year.

Kelly et al (12) recently published age-based reference ranges for annual HV (Figs 2 and 3). They found that although the age of pubertal onset is decreasing, the relationship of growth velocity to SMR remains consistent. Interestingly, they found that AA girls started puberty earlier and had a greater HV between 8.5 and 10.4 years but had slower HV after age 11.5 years. AA boys had greater HV at age 12 years than non-AA boys. Growth and puberty are 99% complete by the time the bone age reaches 17 years.

DELAYED PUBERTY

Delayed puberty is defined as lack of signs of pubertal development at an age 2 to 2.5 SDs above the mean for the population or about 13 years for girls and 14 years for boys. Delayed puberty can be divided into primary and secondary hypogonadism based on circulating concentrations of LH and FSH. Primary hypogonadism is associated with high serum concentrations of LH and FSH, while secondary hypogonadism is associated with low or normal LH and FSH values and can be functional, anatomic, or congenital. Table 2 lists causes of delayed puberty.

Evaluation of delayed puberty involves a careful history and physical examination that includes height, weight, and pubertal staging over time. A thorough history should address nutritional habits, exercise intensity, prior illness, and medications because these can influence the age of onset of puberty. The presence of a midline defect is associated with a higher incidence of GnRH deficiency and may suggest hypogonadotropic hypogonadism. Similarly, neurologic symptoms such as headache, visual disturbances, and anosmia may suggest a central nervous system (CNS) disorder. Extracting a positive family history of constitutional delay of puberty (CDG) or congenital GnRH deficiency is very helpful.

One important step is to determine if pubertal development is totally absent or began and then stopped. Observation of the growth pattern can guide diagnosis. For example, patients with CDG show delayed growth, adrenarche, and sexual development along with declining growth velocity
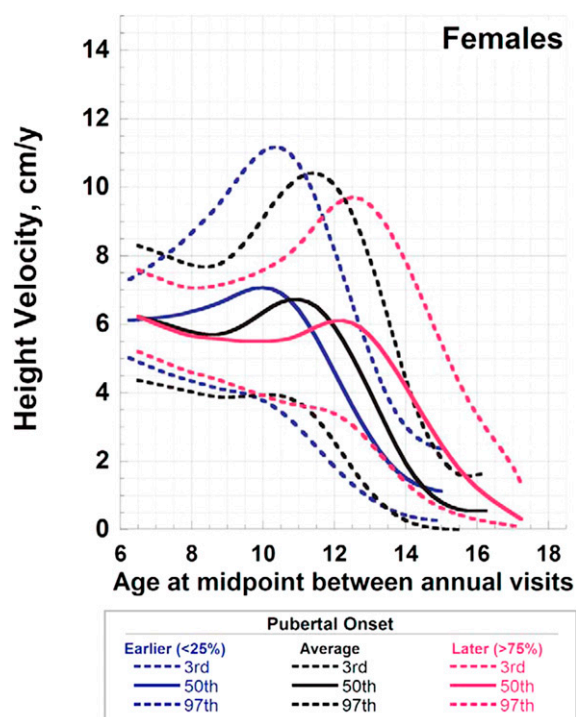

Figure 2. Reference curves for height velocity for female children ages 6 to 17 years according to onset of puberty. Shown are median and the 3rd and 97th percentiles for earlier (blue), average (black), and later (orange) onset of puberty. Earlier puberty was defined as age of onset younger than 9.6 years, average onset as occurring between 9.6 and 11.1 years, and later puberty as onset at age older than 11.1 years. These curves were developed from a large, multicenter, multiethnic, contemporary cohort of children from the United States. Republished with permission of The Endocrine Society, from: Kelly A, Winer KK, Kalkwarf H, et al. Age-based reference ranges for annual height velocity in US children. J Clin Endocrinol Metab 2014; 99:2104. Copyright © 2014 The Endocrine Society; permission conveyed through Copyright Clearance Center, Inc.

and delayed bone age (radiograph of the left hand and wrist). Standing height and weight should be plotted on an appropriate curve and HV should be plotted as well. Arm span can be helpful; an arm span longer than the height by 5 cm suggests delayed epiphyseal closure due to hypogonadism. Testicular size should be measured and the testicles examined for asymmetry because gonadal tumors can occur in several disorders of sex differentiation.

Laboratory testing in delayed puberty should start with assessment of LH, FSH, and estradiol in girls and testosterone in boys. By adolescence, those with primary hypogonadism have elevated LH and FSH values. Patients found to have primary hypogonadism should have a karyotype or comparative genomic hybridization array obtained to evaluate for Klinefelter syndrome in boys (genetic defect due to an extra X chromosome) or Turner syndrome in girls (45XO or mosaic). Additional testing for Fragile X permutation (55-200 CGG repeats in the Fragile X gene [*FMRI*]) should be considered in girls with primary ovarian insufficiency.
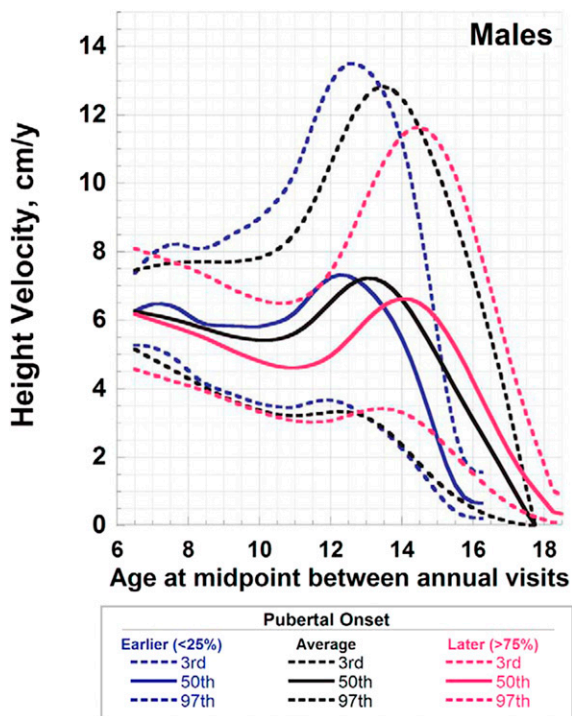
Figure 3. Reference curves for height velocity for male children ages 6 to 19 years according to onset of puberty. Shown are median and the 3rd and 97th percentiles for earlier (blue), average (black), and later (orange) onset of puberty. Earlier puberty was defined as age of onset younger than 10.2 years, average onset as occurring between 10.2 and 11.8 years, and later puberty as onset at age older than 11.8 years. These curves were developed from a large, multicenter, multiethnic, contemporary cohort of children from the United States. Republished with permission of The Endocrine Society, from: Kelly A, Winer KK, Kalkwarf H, et al. Age-based reference ranges for annual height velocity in US children. J Clin Endocrinol Metab 2014; 99:2104. Copyright © 2014 The Endocrine Society; permission conveyed through Copyright Clearance Center, Inc.

Baseline concentrations of LH and FSH are typically low in both CDG and secondary hypogonadism. No single diagnostic test can distinguish CDG from hypogonadotropic hypogonadism other than observation for spontaneous pubertal development by age 16 to 18 years. However, general laboratory testing for delayed or stalled puberty may include assessments driven by history, such as celiac testing, erythrocyte sedimentation rate, comprehensive metabolic panel, and thyroid function. GnRH stimulation testing cannot differentiate between GnRH-deficient patients and those with CDG because of the substantial overlap between LH and FSH responses. Serum prolactin should be measured because hyperprolactinemia can present with arrested puberty. Hypothyroidism can cause delayed puberty. Testing should include both a thyrotropin and free thyroxine because a low/normal thyrotropin value with low free thyroxine could suggest central hypothyroidism due to hypopituitarism. Adrenal androgens may be helpful, such as DHEA-S, because patients with GnRH deficiency are more likely to

have normal adrenal maturation (adrenarche) in contrast to those with CDG, although androgen values in the two groups overlap.

Imaging studies used in the evaluation of delayed or stalled puberty include a bone age radiograph, which allows determination of potential for growth and skeletal maturation as well as prediction of adult height. Serial bone ages can provide continued reassurance about adult height potential. Patients with CDG have bone ages of 12 to 13 years that do not progress further. Delayed or arrested puberty may also present in girls with amenorrhea (absence of menses), which can be primary (no menarche by age 15 years) or secondary (absence of menses for more than 6 months in girls who were previously menstruating). Abdominal ultrasonography may be helpful in girls with delayed puberty to determine the presence of a uterus. The uterus is absent with androgen insensitivity and disorders of Müllerian duct development. Testicular ultrasonography should be ordered if a testicular mass is present. Finally, brain magnetic resonance imaging is indicated if there is evidence for central hormone deficiencies or excess (hyperprolactinemia) and in the presence of neurologic symptoms suggesting a central process.

The most common diagnosis associated with delayed puberty is constitutional delay of puberty (CDG), but this is a diagnosis of exclusion. A retrospective study of clinical and laboratory data from adolescents referred to an academic center for delayed puberty found that CDG was the diagnosis in 53% (63% of males and 30% of females). (13) Delayed but spontaneous pubertal development due to functional hypogonadotropic hypogonadism occurred in 19%, and the causes included growth hormone deficiency, hypothyroidism, hyperprolactinemia, IBD, poor nutrition/poor weight gain, intense exercise, systemic disorders such as juvenile idiopathic arthritis, oncologic diseases, and CNS disorders. Hypogonadotropic hypogonadism was found in 12% and was often permanent due to Kallmann syndrome, Rathke pouch/cleft cyst, hypophysitis, CNS tumor (craniopharyngioma most commonly), or congenital/genetic syndromes. Three percent of cases were unclassified. Interestingly, 10% to 15% of well-documented isolated GnRH deficiency due to Kallmann syndrome undergoes spontaneous resolution after treatment with sex steroids.

INFLUENCES ON TIMING OF PUBERTY

A significant trend toward earlier puberty has now been confirmed by recent studies in both the United States and Europe. Factors associated with earlier puberty include endocrine-disrupting chemicals (EDCs), intrauterine growth retardation, and obesity.

TABLE 2. Causes of Delayed Puberty

PRIMARY HYPOGONADISM (ELEVATED LH AND FSH)

Congenital

- Turner syndrome
- Klinefelter syndrome
- Anorchia (vanishing testes) or cryptorchidism
- Disorder of sex differentiation (androgen insensitivity)

Acquired

- Autoimmune or postinfectious
- Fragile X syndrome
- Due to surgery or trauma
- Iatrogenic (chemotherapy or radiation)

SECONDARY HYPOGONADISM (LOW LH AND FSH)

Congenital

- Isolated GnRH deficiency
- Without anosmia
- Kallmann syndrome
- Due to congenital adrenal hypoplasia
- Prader-Willi syndrome
- Laurence-Moon-Biedl syndrome
- Hypopituitarism (sometimes associated with other midline defects)

Acquired

- Tumors (craniopharyngioma, germinomas, gliomas, astrocytoma)
- Functional
- Constitutional delay of puberty
- Chronic systemic disease
- Acute illness
- Malnutrition (including anorexia nervosa, bulimia)
- Endocrine disorders (hypothyroidism, hyperprolactinemia, DM)
- Infiltrative diseases (hemochromatosis, granulomatous disease, HLH)
- Head trauma
- Pituitary apoplexy
- Drugs (cannabis)

DM=diabetes mellitus, FSH=follicle-stimulating hormone, GnRH=gonadotropin-releasing hormone, HLH=hemophagocytic lymphohistiocytosis, LH=luteinizing hormone.

It is important not to mistake common variation of normal puberty for precocious puberty, most commonly premature thelarche (PT) and premature adrenarche (PA). Girls who have PT often present in the toddler years with isolated breast development but no growth acceleration. Breast tissue typically resolves with no other development of secondary sexual characteristics. PA is a result of elevated adrenal androgens. Affected children are typically taller than expected for mid-parental target height and usually have bone age advance of approximately 2 SDs. In particular, DHEA-S values are elevated but correlate with pubic hair SMR.

An EDC is defined as an exogenous agent that interferes with the synthesis or action of natural hormones and includes some pesticides and plasticizers. Plant-derived phytoestrogens share a chemical structure with estrogen and are found in soy, including soy formula. Lavender oil, tea tree oil, and fennel are other naturally occurring EDCs that have been found to have estrogenic activity. Multiple pediatric endocrine societies have called for further research into EDCs and a possible link with the recent trend toward earlier puberty.

Children born small for gestational age (SGA) or children with birthweights or lengths below -2 SDs are more likely to have precocious pubarche, an earlier onset of pubertal development and menarche, and faster progression of puberty than children born appropriate for gestational age (AGA). Children born SGA generally start puberty at a normal time but relatively earlier than their AGA peers. Their peak HV is reached at a younger age and is shorter than for those born AGA. Those born SGA have earlier skeletal maturation, which may account for shorter adult height. Factors other than birthweight in those who are born SGA that may relate to their pubertal growth pattern include rapid weight gain in early childhood, decreased insulin sensitivity, and increased insulinlike growth factor-1 concentrations. (14)

Nutrition has a powerful influence on pubertal development and can explain as much as 25% of the variation in pubertal timing. (15) Overnutrition and obesity are associated with earlier puberty, while undernutrition is associated with pubertal delay. Children who are obese show increased rates of growth starting in early childhood. Relatively tall stature in obese individuals is typically associated with bone age advance. Obese children usually show a lower peak HV and have been shown to have a decreased growth in height throughout the teenage years. The final height of obese children has been shown to equal that of nonobese children as adults.

It is well established that obesity promotes the onset of puberty in girls, but the data on obesity and male puberty have been conflicting. Previous literature suggested that obesity delays the onset of male puberty, (16) but more recent data suggest that obesity advances the onset of male puberty by about 0.5 years. (17) In a recent study of more than 4,000 Caucasian boys, Tomova et al (18) found earlier enlargement of the testicular volume in overweight and obese boys and earlier pubertal maturation compared to

underweight and normal-weight children. A substantial increase in DHEA-S concentrations occurs during the time when children show the greatest increase in body mass index, which may indicate that body fat strongly influences the activation of adrenal androgen production.

Malnutrition modulates the timing of pubertal development in children and is associated with delayed onset of puberty, reduced pubertal growth spurt, and later age of menarche. Malnutrition can be a result of decreased appetite, eating disorders, increased energy expenditure, and/or malabsorption from disorders such as celiac disease, cystic fibrosis, and IBD. Stunted growth and reduced final height has been reported in children with eating disorders during adolescence, with catch-up growth depending on length of the illness, the type of eating disorder, and when intervention was started.

Growth failure and pubertal delay are associated with IBD. Growth failure seems to be a more prominent feature than delayed puberty and is more common in Crohn's disease (CD) than ulcerative colitis (UC). Many older studies showed delays in the onset of puberty and menarche in patients with CD and UC of about 1.5 years in girls and 0.8 years for boys. However, these studies were conducted at a time when there was heavy reliance on glucocorticoid therapy for CD and UC; more recent studies document more modest delays but continued later age at menarche. (19) As with eating disorders, factors such as age at diagnosis and response to treatment play an important role. Blunted pubertal growth spurts and lower final heights in children with CD have been reported that are seemingly more substantial in boys than girls. However, promising data from Lee et al (16) found that adult heights were not different from the general population, despite a history of growth failure, in those who had CD, suggesting that modern biologic treatments may improve final height in children who have IBD.

GENDER DYSPHORIA IN PUBERTY

The onset of puberty can be a difficult time for individuals with gender dysphoria (GD). GD is a psychiatric diagnosis (*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*) given to individuals with persistent cross-gender identification and discomfort with the gender role of their genetic sex. During infancy and childhood, self-awareness as a specific gender develops and is further shaped by interactions with parents, peers, and the environment. (20) Some hypothesize that prenatal exposure of the brain to sex steroids influences gender identity, but there are many examples where this is not the case. In approximately 75% to 85% of cases, GD does not persist into adolescence or adulthood. (21)

(22) Therefore, it is important that all children and adolescents with GD be evaluated and diagnosed by a mental health professional with experience in child and adolescent developmental psychopathology, and **that no social gender change or hormonal treatment be prescribed in prepubertal children.**

The diagnosis of GD should be based on a complete psychiatric evaluation that is confirmed by the treating endocrinologist. Treatment involves early pubertal suppression with GnRH agonists by SMR 2 to 3 of puberty. Pubertal suppression is followed by initiation of sex steroid treatment to achieve the desired gender at age 16 years and the consideration of sex-changing surgery once the patient is 18 years old. Early pubertal suppression is beneficial because it prevents the physical progression of puberty, which often causes substantial psychological stress on the individual trying to socially live a different gender. Early pubertal suppression has also been associated with better psychosocial and physical outcomes. There are minimal adverse effects to the GnRH agonist treatment, and the therapy is reversible if the child outgrows his or her GD. (22)

Summary

- On the basis of large observational studies and consensus, the normal time for girls to begin puberty is between 8 and 13 years and for boys is between 9 and 14 years.

- On the basis of multiple recent observational studies, there is a secular trend toward earlier puberty in boys and girls. (2)(4)(11)

- Although the triggers for puberty are still not fully understood, recent cohort studies have shown that obesity advances the onset of puberty in girls and possibly in boys. (6)(17)

- On the basis of observational data, menarche is advancing more slowly than thelarche and occurs earlier in girls with elevated body mass index. (4)(6)

- On the basis of observational studies, chronic diseases and malnutrition can delay the onset of puberty. (15)(19)

- Although pubertal onset is occurring earlier, cohort studies have confirmed that the relationship between growth velocity and Sexual Maturity Rating (SMR) has remained consistent. (12)

- On the basis of strong evidence, girls have their pubertal growth spurt earlier than boys, usually between SMR 2 and 3, compared to SMR 3 to 4 for boys.

- Gender dysphoria should be evaluated and managed by a multidisciplinary team with experience in adolescent developmental psychopathology. (20)

CME Quiz and References for this article are at http://pedsinreview.aappublications.org/content/37/7/292.

PIR Quiz

1. You are preparing a medical student to evaluate a 7-year-old Hispanic girl who presents with a chief complaint of breast development. Her past medical history includes low birthweight (40 weeks' gestation, birthweight 2.2 kg) and the onset of obesity around age 2 years. Of the following factors influencing the timing of puberty, you would explain that:

    A. Breast development begins at a later age in African-American and Mexican girls.
    B. Intrauterine growth retardation is associated with delayed onset of puberty.
    C. Obesity delays the onset of puberty in girls.
    D. Pesticides and plasticizers have been implicated in delayed onset of puberty.
    E. Visual inspection is insufficient to distinguish breast tissue from adipose tissue.

2. A 13-year-old boy is concerned because he is now shorter than many of his peers and has no signs of puberty. You would counsel him that the first sign of puberty in boys is typically:

    A. Deepening of the voice.
    B. Development of pubic hair.
    C. Growth spurt.
    D. Increased length of the penis.
    E. Increased testicular size.

3. The mother of a 12-year-old girl reports that her daughter has recently begun to develop pubic hair but has no breast development. She would like to know what signs might help her anticipate her daughter's first menstrual period. In describing the typical progression of puberty, you would explain that:

    A. The growth spurt typically occurs before menarche.
    B. Menarche typically occurs at Sexual Maturity Rating 2 to 3 of breast development.
    C. Menarche usually occurs within 6 to 12 months of the onset of puberty.
    D. Physiologic leukorrhea typically begins 2 to 2.5 years before menarche.
    E. Pubarche is the first sign of puberty in 40% of girls, typically 18 months before menarche.

4. A 6-year-old girl presents with a persistent history of dressing like a boy, preferring boys' activities, and stating that she will grow up to be a man. Gender dysphoria is suspected. An important consideration in the management of this condition is that:

    A. Early pubertal suppression (by Sexual Maturity Rating 2 to 3) with gonadotropin-releasing hormone (GnRH) agonist treatment has been shown to improve psychosocial and physical outcome.
    B. Gender dysphoria persists into adolescence in 75% to 85% of children.
    C. GnRH agonist therapy is not recommended due to an unacceptable adverse effect profile.
    D. GnRH agonist treatment is an irreversible therapy.
    E. Hormonal therapy should be initiated prior to the onset of puberty.

5. A 13-year-old girl is concerned because she has not yet had breast or pubic hair development. Laboratory findings include elevated luteinizing hormone and follicle-stimulating hormone concentrations. Among the following, the most likely diagnosis is:

    A. Congenital adrenal hypoplasia.
    B. Constitutional delay of puberty.
    C. Craniopharyngioma.
    D. Prader-Willi syndrome.
    E. Turner syndrome.

Pubertal Development

Updated Information & Services	including high resolution figures, can be found at: http://pedsinreview.aappublications.org/content/37/7/292
References	This article cites 20 articles, 5 of which you can access for free at: http://pedsinreview.aappublications.org/content/37/7/292.full#ref-list -1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Medical Education** http://classic.pedsinreview.aappublications.org/cgi/collection/medical_education_sub **Journal CME** http://classic.pedsinreview.aappublications.org/cgi/collection/journal_cme **Growth/Development Milestones** http://classic.pedsinreview.aappublications.org/cgi/collection/growth:development_milestones_sub **Endocrinology** http://classic.pedsinreview.aappublications.org/cgi/collection/endocrinology_sub **Puberty** http://classic.pedsinreview.aappublications.org/cgi/collection/puberty_sub **Adolescent Health/Medicine** http://classic.pedsinreview.aappublications.org/cgi/collection/adolescent_health:medicine_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: https://shop.aap.org/licensing-permissions/
Reprints	Information about ordering reprints can be found online: http://classic.pedsinreview.aappublications.org/content/reprints

Pubertal Development

Risa M. Wolf and Dominique Long

The online version of this article, along with updated information and services, is
located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/37/7/292

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®