Regulation and Disorders of Pubertal Timing

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Puberty is a critical human developmental process that leads to sexual maturation and reproductive capability. It requires an intact hypothalamic-pituitary-gonadal (HPG) axis, and any disruption of this axis can result in temporary or permanent disorders of reproductive endocrine function. The HPG axis is active during fetal development and continues to function in infancy until it enters a relative quiescent state, often referred to as the juvenile pause. The factors that mediate the juvenile pause and those that lead to increased gonadotropin-releasing hormone (GnRH) secretion at the onset of puberty are the keys to the regulation of pubertal timing.

Pubertal onset is heralded by the re-emergence of hypothalamic GnRH secretion. GnRH stimulates gonadotrophs in the anterior pituitary to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH) that, in turn, bind to ligand-specific receptors in the gonads, causing gonadal maturation and production of sex steroids, most notably testosterone and estradiol. This process is termed gonadarche. Testosterone and estradiol, together with inhibin, activin, and follistatin, regulate the subsequent activity of the hypothalamus and pituitary gland. The transition from childhood quiescence to the adolescent pattern of GnRH secretion is a gradual process, and LH and FSH pulsatility has been detected in normal children as young as 4 years of age [1,2]. Throughout childhood, GnRH secretion appears to undergo small but progressive increases until the onset
of puberty, when GnRH secretion increases, first at night and eventually throughout the day.

**Adrenarche**

The physical changes of puberty result from both gonadarche and adrenarche. Adrenarche refers to the maturation of the zona reticularis of the adrenal gland, resulting in increased production of adrenal androgens associated with secondary sexual characteristics such as the development of pubic hair (pubarche), axillary hair, body odor, and acne. Adrenarche typically begins at the age of 8 years, but can occur as early as 6 years [3,4]. Like gonadarche, the onset of adrenarche appears to be a gradual, progressive maturational process that begins in early childhood and is marked by further increases in the production of adrenal androgens (DHEA, DHEA-S, androstenedione) around the time of puberty [5]. Adrenarche may precede gonadarche by 1 to 2 years in boys and girls, but the timing of clinical signs can vary. Although adrenarche and gonadarche often overlap, they are separate processes that are regulated independently [6–8]. The triggers for adrenarche remain unknown; however, alterations in body weight and body mass index (BMI) and in utero and neonatal physiology likely modulate the developmental process [9,10].

**Timing of pubertal onset**

The onset of puberty occurs across a wide range of ages in normal, healthy adolescents. Several pathologic states influence the timing of puberty directly or indirectly and contribute to this splay, but most of the variation in pubertal timing cannot be attributed to any clinical disorder. Rather, much of the variation in the timing of pubertal onset stems from differences in the maturational program of GnRH secretion.

**Controversies surrounding current estimates of pubertal onset**

Precocious puberty traditionally has been defined by the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. This definition was based primarily on the series published by Marshall and Tanner, in which observers used sequential photographs taken every 3 months of British adolescents to rate breast and pubic hair development in females and genital and pubic hair development in males [11,12]. In those studies, females displayed breast development (the most common first sign of puberty) at a mean age of 11.2 ± 1.1 years while pubertal maturation in males (increase in testicular volume) occurred at the slightly later mean age of 11.6 ± 1.1 years. Ninety-five percent of girls experienced onset of breast or pubic hair development between the ages of 8.5 and 13 years, with menarche occurring at an average age of 13.5 ± 1.0 years, while 95% of boys began genital development between 9.5 and 13.5
years. These ranges were in agreement with several other studies, including those of United States youth [13–15].

Although there had been a secular trend toward earlier pubertal development [16], the timing of puberty in developed countries was thought to be fairly stable over the ensuing decades, until recent data questioned whether the trend toward earlier pubertal development had continued. In 1997, Herman-Giddens et al published cross-sectional data from over 17,000 females, aged 3 to 12 years, studied within the Pediatric Research in Office Settings (PROS) network [17]. In this study, girls seen for a health supervision or problem visit were inspected visually to assess breast and pubic hair development. Their data suggest that girls in the United States are undergoing pubertal development at younger ages than previously reported. In white girls, the mean age for attainment of Tanner 2 breast development was 10.0 ± 1.8 years, while Tanner 2 pubic hair began at a mean age of 10.5 ± 1.7 years. In African-American girls, onset of puberty occurred even earlier, with a mean of 8.9 ± 1.9 years for Tanner 2 breast development and 8.8 ± 2.0 years for Tanner 2 pubic hair. Additionally, 6.7% of white and 27.2% of African-American girls had evidence of breast or pubic hair development before the age of 8 years, indicating that application of traditional definitions would result in a high proportion of girls being diagnosed with precocious puberty.

These findings prompted suggestions to change the age limit and evaluation for precocious puberty [18]. In 1999, the Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society (LWPES) published new recommendations suggesting the age cutoff for precocious puberty should be decreased to 7 years in white girls and 6 years in African-American girls [18]. This report did recommend that white girls with breast development after age 7 or African-American girls with breast development after age 6 years should undergo evaluation if: the tempo of pubertal progression is abnormal resulting in a bone age advanced more than two years and a predicted height that is either less than 150 cm (59 in) or two SD below the genetic target height; headaches, focal neurologic deficits, or an underlying neurologic problem are present; or the child’s or family’s emotional state is affected adversely by the progression of puberty and potential for early menarche.

The proposed recommendations for redefining the age limit of precocious puberty led to substantial controversy [19–24]. The first question was the accuracy of the PROS data regarding normal pubertal development in girls. In an era of increasing obesity, could fatty tissue have been interpreted as breast development? Were the children studied truly a random sample of United States youth, or was there ascertainment bias? Without details of endocrinologic evaluations for girls who were younger than 8 years when puberty began, is it certain that these children did not have any underlying pathology? Why is it that the age of breast development decreased substantially, but the average age of menarche (12.9 ± 1.2 years in white
girls, 12.2 ± 1.2 years in African-American girls) occurred at a similar age compared with other recent studies? The authors and others have tried to address many of these issues [20,21,24–27], but uncertainties remain. In support of the PROS data, other studies have shown differences in pubertal development among different ethnicities and a trend toward earlier pubertal development; however, the timing of puberty was not as early as reported in Herman-Giddens et al [28,29]. It is also interesting that a study of Spanish youth reported differences in duration of sexual maturation depending on the timing of breast development, with girls experiencing earlier onset of breast development having a longer duration before the onset of regular menses than girls with later breast development [30].

The second controversy is whether implementation of the proposed LWPES guidelines would result in failure to identify young girls with underlying pathology. Several retrospective cohort studies have described cases of astrocytomas, gliomas, adenomas, craniopharyngiomas, hamartomas, congenital adrenal hyperplasia, and McCune-Albright syndrome that may have been missed using the new LWPES guidelines [31–33]. These data have led some to hold to the recommendation that all girls with pubertal onset before age 8 years have a complete evaluation including a head MRI [34,35].

It is clear that additional, well-designed, large prospective studies are needed to define further the normal ages of pubertal development and the rates of pathology among 6- to 8-year olds before definitive conclusions can be made regarding the definition of precocious puberty and the extent of any needed evaluation. As illustrated in Fig. 1, both pieces of information are important to clinical practice. For example, if hypothetically, the absolute

Fig. 1. Factors affecting the proportion of 7- to 8-year-old girls with pathologic causes of early puberty. The timing of puberty is a normally distributed trait. There will, therefore, be some biologically/physiologically normal individuals with pubertal onset below the statistically defined limit (ie, 2–2.5 SD below the mean). There also will be children below the age limit who have precocious puberty secondary to underlying pathology. Knowing the proportion of children under the age cutoff with idiopathic versus pathologic causes for precocious puberty would help to determine who should be evaluated. (A) Effect of shift in mean for the general population. A change in the statistically accepted mean and range of normal pubertal timing in the general population could affect the proportion of 7- to 8-year-old girls with underlying pathology. (B) Effect of different numbers of pathologic cases. A change in the number of pathologic cases also affects the proportion of 7- to 8-year-olds with underlying pathology.
number of girls with a pathologic cause for pubertal development between 7 and 8 years was constant, the proportion of 7- to 8-year-old girls with pubertal development secondary to an underlying disorder would vary depending on the number of girls within the general population who experience puberty before age 8 (see Fig. 1A). Similarly, the proportion of normal versus pathologic cases would depend on the background number of pathologic cases (see Fig. 1B). Pending new data regarding normal age of pubertal onset and rates of pathology, the authors still perform a complete evaluation in all girls with pubertal onset younger than 6 years and in most girls with onset between the ages of 7 and 8.

There is some, but much more muted, controversy over the age of normal pubertal development and the definition of precocious puberty in boys. Based on an analysis of National Health and Nutrition Examination Survey (NHANES) III data, where genital ratings were performed by visual inspection, Herman-Giddens et al reported mean Tanner 2 genital development occurring at 10.1 ± 0.5 years in white boys, 9.5 ± 0.6 years in African-American boys, and 10.4 ± 0.8 years in Hispanic boys [36]. Using the traditional cutoff of 9 years, these data suggest that large numbers of boys would be classified as having precocious puberty. Questions have been raised regarding the criteria used for genital staging [19,37], however, and the analysis also contrasts with other data from the 1990s that found pubertal timing to be similar to previous standards [38]. Interestingly, in a separate analysis of the NHANES III data, Sun et al found mean ages at entry into Tanner 2 genital development of 11.08 ± 0.18 SEM years in white boys, 10.79 ± 0.13 years in African-American boys, and 11.09 ± 0.17 years in Hispanic boys [28]. These mean numbers are not that different from the traditional norms, but the median values were much younger and were similar to those reported in the 2001 Herman-Giddens et al analysis. The reasons for the difference between mean and median values deserve further study. However, because of uncertainties about the data [19,37], perhaps because a trend toward earlier pubertal development among boys resonates less strongly with daily clinical experience, and perhaps because a higher proportion of boys than girls with precocious puberty have underlying pathology, there have not been general calls to decrease the age limits for normal pubertal development among boys.

**Regulation of pubertal timing**

Pubertal timing is correlated highly within ethnic population groups, within families, and between monozygotic twins, with heritability estimates suggesting that 50% to 80% of the variation in pubertal timing is determined by genetic factors [39–41]. It is important to note that this genetic component does not preclude a significant role for environmental influences that may have changed over time. For example, the mean age of menarche in mid-nineteenth century Europe was likely between 17 and 18.
years [42], but a clear shift toward earlier menarche subsequently occurred [39], presumably because of improved nutrition and health standards [16]. Within a given population at a given moment in time, however, much of the variation in pubertal timing is caused by genetic factors.

**Insights from single gene disorders**

Identification of genes that lead to hypogonadotropic hypogonadism (HH) has provided much insight into the development and regulation of the HPG axis [43–45]. For example, mutations in KAL lead to X-linked Kallmann's syndrome and demonstrate the importance of anosmin to GnRH neuronal migration during embryogenesis. Mutations in fibroblast growth factor receptor 1 (FGFR1) recently were linked to an autosomal-dominant form of Kallmann’s syndrome [46], indicating that a whole new pathway likely is involved in GnRH neuronal development. The importance of nutrition in modulating HPG axis activity is evidenced by the HH that results from defects in leptin or in the leptin receptor. These and other data have led to speculation that leptin is a trigger for pubertal onset [47], but a more widely held view is that leptin plays a more permissive role in regulating the onset of puberty [41]. Other causes of HH include mutations in genes that are critical to hypothalamic-pituitary development, including dosage-sensitive sex reversal adrenal hypoplasia congenital (DSS-AHC) critical region on the X chromosome (DAX1), steroidogenic factor 1 (SF-1), and several pituitary transcription factors such as HESX-1, LHX3, and PROP-1. It is also apparent that prohormone convertase 1 (PC1) is important in the processing of GnRH, since mutations in this enzyme also lead to HH. The recent finding that mutations in GPR54, a G protein-coupled receptor, cause HH [48,49] identifies an important new pathway that regulates GnRH secretion.

This information is important and exciting, but the role that the genes (and pathways) identified by these disorders play in regulating the timing of puberty in healthy adolescents remains unclear. Certainly, less severe genetic variation (polymorphisms) in any of these genes could help explain the variation in pubertal timing seen within the general population, but no associations between genetic variants and normal variation in pubertal timing have yet been reported.

**Neuroendocrine regulation of pubertal onset**

Understanding what factors contribute to the dampening of the HPG axis after infancy and what factors lead to the pubertal re-emergence of GnRH secretion is critical to understanding the regulation of pubertal timing. Gamma-amino butyric acid (GABA) neurons appear to play a prominent role in inhibiting prepubertal GnRH release [50]. There is evidence that GABA also can stimulate GnRH secretion, but this variable
action may be dependent on developmental stage, variability in GABA receptor, and expression of KCC2 (a protein that can alter the inhibitory and excitatory properties of chloride channels) [51]. The recent finding that neuropeptide Y (NPY) mRNA expression in the hypothalamus of juvenile monkeys is higher than neonatal animals suggests that NPY may play a role in the juvenile pause [52]. Other factors that likely play a role in inhibiting GnRH release include endogenous opioids (ie, β-endorphin) and melatonin, but neither of these compounds likely plays a major role in regulating the timing of puberty [53].

The principal excitatory neurotransmitter in the hypothalamus is glutamate, an important stimulator of GnRH secretion through its actions at the N-methyl-D-aspartate and kainate receptors. Other stimulators of GnRH secretion include leptin, norepinephrine, dopamine, tumor growth factor–α, kisspeptins (that bind to GPR54), neuregulin signaling by means of erbB4 receptors, and galanin-like peptide [41,53–56]. It is postulated that many of these neurotransmitters act by means of a complex, intricate communication network that exists between glial cells and neurons within the hypothalamus [57]. The potential role that these and other compounds play in regulating the onset of puberty remains an area of active investigation.

**Obesity and the relationship to pubertal timing**

The relationship between nutritional status and pubertal onset has been the focus of much investigation [39,41]. With the recent increases in obesity among youth, one wonders if increased adiposity has contributed to the possible shifts toward earlier puberty. Within the PROS data, significantly higher BMI scores were found among pubertal girls between the ages 6 and 9 compared with age- and gender-matched prepubertal girls [26]. Biro et al, in an analysis of data from the National, Heart, Lung, and Blood Institute Growth and Health Study, found that girls with earlier onset of menarche (< 20th percentile for race) also had the greatest average BMI SD score when compared with girls with normal or late menarche [58]. In another analysis of the NHANES III data, girls with earlier onset of breast development were more likely to be overweight or obese [59]. Interestingly, the same study found the opposite trend in boys; that is, obesity was more prevalent in boys with later genital maturation, suggesting that male pubertal development may be less sensitive to nutritional status. Overall, these studies suggest a relationship between increasing levels of adiposity and earlier sexual maturation in girls, but whether such an association is causal has not been established.

**Endocrine disruptors and environmental influences**

Synthetic and naturally occurring substances that alter normal reproductive development and function are known as endocrine-disrupting
chemicals (EDC). Several environmental agents, including polychlorinated biphenyls, organochlorine pesticides, and phthalates, have been implicated as EDCs [60]. These industrial chemicals may affect the reproductive systems of exposed animals by binding estrogen receptors and altering GnRH gene expression [60]. Data in humans are limited, but there are examples of possible associations between phthalates, an industrial compound with estrogenic activity, and premature thelarche in young girls [61] and precocious puberty in young girls exposed to cosmetics or hair care products containing synthetic and naturally occurring estrogen-like chemicals [62]. It also has been hypothesized that naturally occurring, soy protein-based phytoestrogens, found in high levels in soy-based infant formulas, could lead to altered pubertal maturation [63]. Although these individual examples are interesting, and some have suggested that shifts toward earlier pubertal development could stem from EDC exposure [17], no evidence for a widespread link between EDC exposure and altered pubertal timing has been identified [64]. This is an important area for future research, and should any causal effects be demonstrated, it would be important to determine whether the effects of EDCs are limited to earlier development of secondary sexual characteristics (ie, early breast development caused by estrogen or estrogen-like effects) or whether EDCs can alter the timing of HPG axis maturation.

Precocious puberty

Complete precocious puberty results from centrally (GnRH-dependent) or peripherally (GnRH-independent) mediated processes and is distinct from incomplete or partial precocity, which is limited to either signs of adrenarche or thelarche. Precocious pubertal development may be isosexual (secondary sexual characteristics consistent with gender) or contrasexual (secondary sexual characteristics inconsistent with gender). The distinctions among these various categories have important implications for diagnostic evaluations and therapy.

Centrally mediated precocious puberty

Centrally mediated precocious puberty (CPP) results from activation of the HPG axis and early gonadarche. As in normal puberty, breast development is the most common initial physical sign in females, although girls can present with development of pubic hair or menses. Males display the symmetrical increase in testicular volumes indicative of gonadarche and the physical changes associated with testosterone exposure. In girls, CPP is most often idiopathic, but a broad range of neurogenic causes must also be considered (Box 1). Boys also have idiopathic CPP, but they are at greater risk of having underlying pathology. Estimates vary greatly, but
### Box 1. Common etiologies of precocious puberty

**Central (GnRH-dependent)**
- Idiopathic
- Central nervous system (CNS) tumors
  - Hamartomas
  - Astrocytomas
  - Adenomas
  - Gliomas
  - Germinomas
- CNS infection
- Head trauma
- Iatrogenic
  - Radiation
  - Chemotherapy
  - Surgical
- Malformations of CNS
  - Arachnoid or suprasellar cysts
  - Septo-optic dysplasia
  - Hydrocephalus
  - Empty sella syndrome

**Peripheral (GnRH-independent)**
- Congenital adrenal hyperplasia
- Testosterone/estrogen-producing tumors
  - Adrenal/ovarian carcinoma or adenoma
  - Granulosa cell tumor
  - Theca cell tumor
  - Leydig cell tumor
- Gonadotropin/hCG-producing tumors
  - Choriocarcinoma
  - Dysgerminoma
  - Hepatoblastoma
  - Chorioepithelioma
  - Teratoma
  - Gonadoblastoma
- Exogenous exposure to androgen/estrogen
- Familial male–limited precocious puberty
- McCune-Albright syndrome
- Ovarian cysts
- Hypothyroidism (Van Wyk-Grumbach syndrome)
- Aromatase excess syndrome
approximately 85% of CPP in girls is idiopathic, while approximately 60% of males have pathologic causes [32,35,65–68].

*Peripherally mediated precocious puberty*

Peripheral precocious puberty occurs much less frequently than CPP [67] and does not involve activation of the HPG axis. The distinction between CPP and peripheral precocious puberty is not always complete, since in some cases (McCune-Albright syndrome and congenital adrenal hyperplasia, for example) secondary development of CPP also can occur. This may stem from early exposure to (and perhaps withdrawal from) sex steroids altering regulation of the HPG axis. Recognizing this potential complication of peripheral precocious puberty is important to successful therapy.

*Incomplete, unsustained, and intermittent forms of sexual precocity*

Girls with premature thelarche usually present during the first two years of life. The sexual development is not progressive and is not associated with substantial bone age advancement, signs of androgen production, or compromised adult height. The cause of premature thelarche is unclear, although girls with premature thelarche may have increased estradiol levels compared with controls [69]. Occasionally, premature thelarche can be an early stage of HPG axis maturation [70] that progresses to CPP [71].

Premature adrenarche also is not associated with progressive pubertal development. Several pathologic disorders, however, such as late-onset congenital adrenal hyperplasia or testosterone-secreting tumors, can present as premature adrenarche, highlighting the importance of close clinical and laboratory monitoring. Premature pubarche often is associated with obesity and acanthosis nigricans indicative of underlying hyperinsulinemia, and an association between premature pubarche and subsequent risk of polycystic ovary syndrome and the metabolic syndrome has emerged [3,72].

Some cases of early pubertal development are characterized by unsustained, intermittent, or slowly progressive development. The etiology of this type of development is unclear, although there is evidence that some cases may represent intermittent HPG axis activation [73]. More recently, mutations in Gs-α have been identified in young girls with fluctuating, exaggerated thelarche, and this may represent another cause of intermittent pubertal development [74].

*Diagnostic evaluation of the child with complete precocious puberty*

The evaluation of a child with precocious puberty is summarized in Box 2. Clinically, true precocity is marked by significant bone age advancement (> 2 SDs for age), a recent history of growth acceleration, and a progression of secondary sexual characteristics on physical examination. Peripheral causes of precocious puberty are characterized by suppressed LH and FSH
values in the setting of elevated testosterone or estradiol levels. Historically, GnRH stimulation testing and the demonstration of pubertal gonadotropin responses have been the gold standard for diagnosis of CPP. Given the current unavailability of GnRH, however, alternative strategies must be considered. These include measurement of spontaneous LH levels using highly sensitive immunochemiluminometric assays [75], use of ultrasensitive estradiol assays [76], ultrasonographic measurement of ovarian and uterine lengths [77], or stimulation of the pituitary-gonadal axis with subcutaneous nafarelin [78] or leuprolide [79–81] and monitoring LH response. Additional replication of initial results and further delineation of normal and abnormal responses in large numbers of children are needed to determine the optimal use of these alternative strategies.

Premature thelarche and premature adrenarche typically are characterized by prepubertal gonadotropin levels, minimal to no increase in testosterone or estradiol levels, and no or minimal bone age advancement. Children with premature adrenarche commonly present with DHEA and DHEA-S levels in an early pubertal range. Most importantly, advancement in physical maturation and bone age typically does not occur in either of these conditions until an appropriate pubertal age.

Consequences of precocious puberty

Because epiphyseal fusion is an estrogen-dependent process, early production of sex steroids can cause rapid advancement of skeleton maturation and result in compromised final adult height. Short stature is

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Box 2. Evaluation of precocious puberty

Common initial screening tests
- Careful history, physical exam, and assessment of growth velocity
- Bone age
- LH, FSH
- Estradiol, testosterone
- DHEA-S
- 17-Hydroxyprogesterone
- TSH, T4

Secondary tests to consider
- Pelvic ultrasound
- MRI of head
- β-hCG
- GnRH or leuprolide stimulation test
- ACTH stimulation test
most pronounced in those children with earlier onset of symptoms and more shortened prepubertal growth periods [82]. Recently, Weise et al suggested that growth plate senescence also may contribute to poorer height outcomes [83]. Psychosocial stresses related to pubertal development and menarche at a very young age are additional consequences of precocious puberty. Overall, most children with precocious puberty do well, but there are some reports of increased psychosomatic complaints, depression, and anxiety in females [84,85].

**Therapeutic options in precocious puberty**

Children with incomplete forms of early pubertal development do not require therapy, but they should be monitored to ensure their development is not progressive. Unsustained, intermittent, or slowly progressive forms also may not necessitate therapy [73,86].

The goal of therapy in CPP is to preserve adult height and alleviate potential psychosocial effects of precocious puberty. GnRH agonists remain the mainstay of treatment for centrally mediated precocious puberty. Administration of these agents down-regulates the pituitary–gonadal axis and limits pubertal progression. Various formulations (intramuscular, subcutaneous, and intranasal) of short- (daily) and long- (monthly) acting GnRH agonists are available, with depot leuprolide being the most commonly used preparation in the United States. Newly developed 3-month depot formulations also have been shown to be effective [87,88].

Gonadotropin-releasing hormone agonists have been shown to improve adult height compared with pretreatment predicted height in children with CPP [89,90], but outcomes are variable with children younger than 6 at initiation of therapy gaining the most height and those over 8 showing little benefit [18,90]. GnRH agonists generally are tolerated well, but occasionally, an initial, temporary flare of GnRH activity can occur and result in transient advancement of secondary sexual characteristics and even vaginal bleeding. Initial concerns about long-term effects of GnRH agonists on bone mineral density have been alleviated [91], and although there are contradictory data [91,92], it appears that GnRH agonist therapy does not lead to obesity beyond that predicted by baseline, pretreatment status.

Monitoring of GnRH agonist therapy entails careful attention to skeletal maturation, growth velocity, secondary sexual characteristics, gonadotropin levels, sex steroid levels, and response to GnRH stimulation testing. With the unavailability of GnRH, an alternative is to measure LH either 30 to 60 minutes [93] or 2 hours [81] after a therapeutic leuprolide injection. The optimal time to discontinue GnRH agonist therapy is unclear and difficult to determine because of variability in chronologic age, bone age, and duration of symptoms when therapy was initiated. These issues, along with long-term studies of reproductive function, are important areas for further study.
Treatment of peripheral precocious puberty involves treating the underlying disorder and limiting the effects of elevated sex steroids. This may involve use of ketoconazole (steroidogenesis inhibitor), spironolactone (androgen receptor inhibitor), testolactone and anastrozole (aromatase inhibitor), and tamoxifen (estrogen receptor inhibitor). Recently, tamoxifen has shown particular promise for treatment of McCune-Albright Syndrome [94], but long-term efficacy and safety data are needed.

Delayed puberty

Delayed puberty is defined as the absence of secondary sexual characteristics by an age that is 2 to 2.5 SDs beyond the mean for the population (approximately age 13 years in girls and 14 years in boys). The most common cause of pubertal delay (and the focus of this discussion) is constitutional delay of growth and maturation (CDGM), but many other etiologies must be considered (Box 3 and Fig. 2), especially in girls, in whom CDGM is less prevalent. In addition to CDGM, delayed puberty can result from permanent hypogonadotrophic hypogonadism, the reversible or functional hypogonadotrophic hypogonadism that is associated with delayed but spontaneous pubertal development in the setting of an underlying condition or systemic illness, or permanent hypergonadotrophic hypogonadism. In a recent case series of 232 youths with delayed puberty, 50 different underlying etiologies were identified [95].

Constitutional delay of growth and maturation

Individuals with CDGM have no underlying condition that causes pubertal delay and eventually undergo spontaneous pubertal development. Most analyses suggest that CDGM is male-predominant, but that may stem, at least in part, from ascertainment bias [95,96]. Youth with CDGM usually have low or normal BMI scores and short stature, which has led some to suggest that CDGM is associated with low leptin levels [97]. There is increasing awareness, however, that some boys with CDGM are obese [95,98]. It remains to be determined whether this group is simply representative of the increasing obesity trend among adolescents or if physiologic mechanisms different from those present in CDGM account for the pubertal delay.

Because CDGM may represent the extreme end of the normal spectrum of pubertal development, further understanding of this condition likely will improve understanding of the mechanisms that regulate pubertal timing in people. CDGM long has been known to aggregate in families, but recent analyses have focused additional attention on the genetic nature of this condition. Of note, boys and girls with CDGM often have positive family histories for delayed puberty, and both the mother and father contribute to the genetic predisposition in both genders [95,99]. In addition, many family
Box 3. Common etiologies of delayed puberty

Functional hypogonadotrophic hypogonadism

Systemic illness
- Cystic fibrosis
- Asthma
- Inflammatory bowel disease
- Celiac disease
- Juvenile rheumatoid arthritis
- Anorexia nervosa/bulimia
- Sickle cell disease
- Hemosiderosis
- Thalassemia
- Chronic renal disease
- AIDS

Endocrinopathies
- Diabetes mellitus
- Hypothyroidism
- Hyperprolactinemia
- Growth hormone deficiency
- Cushing syndrome

Excessive exercise
Malnutrition

Permanent hypogonadotrophic hypogonadism

CNS tumors/infiltrative diseases
- Astrocytoma
- Germinoma
- Glioma
- Craniopharyngioma
- Prolactinoma
- Histiocytosis X

Genetic defects
- KAL, FGFR1 (Kallmann’s syndrome)
- GnRHR, GPR54, DAX1, PROP1
- Leptin/leptin receptor deficiency

Syndromes
- Prader-Wili
- Lawrence-Moon-Bardet-Biedl
- Multiple lentigines/LEOPARD
- CHARGE
- Gaucher disease

Post-CNS infection
histories are consistent with an autosomal-dominant inheritance with variable penetrance. This finding suggests that some of the variation in the timing of puberty within the general population may stem from variation in a few genes with major effects. These findings are in agreement with a study reporting that 37% of the genetic contribution to the age of menarche is caused by dominant effects [100] and a recent analysis demonstrating that precocious puberty also can be dominantly inherited [101].

It generally is accepted that most boys with CDGM will grow to a height considered normal for the general population [96]. Several studies, however, have shown that boys with CDGM often fail to reach their midparental target heights [102,103] and their predicted heights based on prepubertal bone ages [104]. The etiology for the decrease in adult height is unclear. Individuals often have lower growth hormone levels than expected for chronologic age but respond to endogenous or exogenous sex steroids with appropriate increases in growth hormone secretion [105,106]. It also has

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<td>* Septo-optic dysplasia</td>
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Chemotherapy/radiation therapy

Trauma

**Permanent hypergonadotrophic hypogonadism**

Genetic syndromes

* Klinefelter’s syndrome
* Turner syndrome
* Noonan syndrome

Cryptorchidism

Gonadal dysgenesis

Vanishing testes syndrome

Trauma/testicular torsion

Chemotherapy/radiation therapy

Gonadal infection

* Mumps, coxsackie

Galactosemia

Autoimmune oophiritis

Biosynthetic defects

* 5-α-Reductase deficiency
* 17,20 lyase deficiency
* Congenital lipoid adrenal hyperplasia

Androgen insensitivity

Sertoli cell only syndrome (Del Castillo syndrome)
been shown that shorter boys with CDGM have a shorter sitting height, more pronounced eunuchoid body habitus, and decreased upper to lower segment ratio [104]. This physical appearance may be more predictive of short stature as an adult.

Puberty is a critical period for accrual of bone mineral content. Thus, several studies have evaluated the hypothesis that CDGM results in decreased bone mineral density. One study suggested an increased risk for low areal bone mineral densities (aBMD) in a cohort of men with a history of CDGM [107]. Because smaller bone size can influence standard dual energy radiograph densitometries, resulting in low aBMD, two follow-up studies measured volumetric bone mineral density (vBMD) in separate cohorts of men with CDGM [108,109]. Both of these analyses suggested that vBMD was normal and found no difference attributable to androgen therapy during adolescence. The second study, however, did find that adult males with a history of CDGM may have decreased total bone mass, but this is of unclear significance [109].

In general, individuals with CDGM fair well, but the delayed puberty or short stature associated with CDGM can be a source of anxiety and emotional stress [110]. One group has reported a tendency toward psychopathology (substance abuse and disruptive behavior) during the transition to adulthood among individuals with CDGM [85].

Functional hypogonadotropic hypogonadism

Causes of functional hypogonadotropic hypogonadism are listed in Box 3. Unlike permanent hypogonadotropic hypogonadism or hyper-
gonadotropic hypogonadism, individuals with functional hypogonadotropic hypogonadism tend to be male and more often have a positive family history of delayed puberty [95]. These characteristics are similar to CDGM and raise the possibility that in some subjects with functional hypogonadotropic hypogonadism, the physiology underlying pubertal delay is, in part, similar to CDGM. One also questions whether the defects that lead to the development of the underlying disorder may, in and of themselves, cause delayed puberty. For example, puberty often is delayed in youth with cystic fibrosis. This delay is likely multifactorial and related to nutritional state, inflammation, and the degree of pancreatic endocrine or exocrine insufficiency [111]. Some cystic fibrosis patients with good nutrition and clinical status, however, have delayed menarche [112], raising the possibility that abnormalities in the cystic fibrosis transmembrane conductance regulator (CFTR) gene may affect the HPG axis directly [113].

**Diagnosis of delayed puberty**

Constitutional delay of growth and maturation is a diagnosis of exclusion, and the other etiologies for pubertal delay (see Box 3) must be considered. A typical evaluation is described in Box 4. The most challenging distinction to make is that between CDGM and permanent hypogonadotropic hypogonadism. The definitive diagnosis of CDGM requires demonstration of spontaneous pubertal development, yet one would like to separate CDGM from hypogonadotropic hypogonadism during the initial evaluation. Gonadotropin responses to short- [114] and long-[115,116] acting GnRH agonists have been proposed as effective discriminators. Further study and additional definition of the characteristic CDGM and hypogonadotropic hypogonadism responses, however, are needed to assess the clinical applicability of these tests fully.

**Therapy for delayed puberty**

The goal of therapy in boys with CDGM is to induce secondary sexual characteristics and growth acceleration without adversely affecting final height or suppressing the maturation of the HPG axis. Testosterone esters such as testosterone enanthate, cypionate, or propionate most commonly are used, and a low dose of 50 mg intramuscularly each month for 3 to 6 months is effective [117,118]. Oxandrolone, a less commonly used 17α-alkylated nonaromatizable anabolic steroid, has been shown to accelerate growth velocity in boys with CDGM without compromising final adult height [119–121]. Oxandrolone’s use, however, is limited by rare, but significant hepatotoxicity and a limited ability to promote physical signs of pubertal maturation. Testosterone patches and gels are alternative treatment options, but their use has been limited by the requirement for low doses. The use of testosterone gels to initiate pubertal development is
being studied and may become more widespread, but one must be aware that gel preparations can result in unwanted virilization in family members and other physical contacts [122,123].

The use of aromatase inhibitors in boys with CDGM is recent and intriguing. One rationale for aromatase inhibitor therapy is that limiting conversion of testosterone to estrogen would delay epiphyseal maturation and increase final height. In a recent randomized, double-blind, placebo controlled trial, boys receiving a fourth-generation aromatase inhibitor (letrozole) plus testosterone for 1 year had decreased estrogen levels, increased testosterone levels, and increased predicted final adult height compared with the control group (testosterone plus placebo) [124]. In addition, LH and FSH levels rose significantly in the aromatase inhibitor group compared with the control group, consistent with a role for estradiol in inhibiting gonadotropin release in pre/early pubertal males. Although initial results are promising [125], aromatase inhibitor therapy requires future, larger-scale prospective studies in children with CDGM to assess its impact on final adult height outcomes, pubertal tempo, and other estrogen-specific effects such as changes in bone mineral density. Treatment of permanent hypogonadotropic hypogonadism and hypergonadotrophic hypogonadism

<table>
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<tr>
<th>Box 4. Evaluation of delayed puberty</th>
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<td>LH levels following GnRH agonist</td>
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with testosterone is similar to therapy for CDGM except that doses gradually are increased to full adult replacement. In men (and women) with permanent hypogonadotropic hypogonadism, gonadotropin therapy or pulsatile GnRH can be used to induce fertility.

Several estrogen supplements are available to initiate normal pubertal changes and menstrual cycling in females with hypogonadism. Common treatment regimens include oral equine estrogens or ethinyl estradiol at low doses that promote secondary sexual characteristics without causing accelerated maturation of epiphyseal plates. In permanent hypogonadism, the dose of estrogen is slowly increased over 12 to 24 months to an adult replacement dose, and endometrial cycling usually is initiated after approximately 12 months of unopposed estrogen therapy. Transdermal estrogens (17-B-estradiol) provide an excellent alternative to traditional oral regimens. Transdermal preparations do not undergo first-pass metabolism in the liver, which may reduce the risk for coagulopathy and subsequent venous thromboembolic disease that is a concern with oral preparations [126,127]. Another advantage of transdermal systems is that the matrix patch can be subdivided to deliver low doses, initially only at night, and mimic more effectively normal physiology [128]. A similar strategy was reported recently using percutaneous estrogen gel to initiate puberty in girls with Turner Syndrome [129].

Summary

The factors that determine the onset of puberty remain elusive. New discoveries about HPG axis regulation will enhance understanding of normal variation in pubertal timing and likely provide further insight into pubertal disorders.

References

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