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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

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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 $\pm$ 1.1 years while pubertal maturation in males (increase in testicular volume) occurred at the slightly later mean age of 11.6 $\pm$ 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 $\pm$ 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 $\pm$ 1.8 years, while Tanner 2 pubic hair began at a mean age of 10.5 $\pm$ 1.7 years. In African-American girls, onset of puberty occurred even earlier, with a mean of 8.9 $\pm$ 1.9 years for Tanner 2 breast development and 8.8 $\pm$ 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 $\pm$ 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

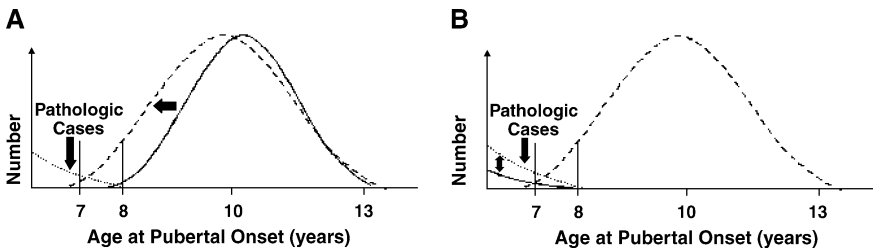

Fig. 1. Factors affecting the proportion of 7- to 8-year-old girls with pathologic causes of early puberty. The timing of puberty is a normally distributed trait. There will, therefore, be some biologically/physiologically normal individuals with pubertal onset below the statistically defined limit (ie, 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 $\pm$ 0.5 years in white boys, 9.5 $\pm$ 0.6 years in African-American boys, and 10.4 $\pm$ 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 $\pm$ 0.18 SEM years in white boys, 10.79 $\pm$ 0.13 years in African-American boys, and 11.09 $\pm$ 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

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

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], ultrasonaographic 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

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 hypogonadotropic hypogonadism, the reversible or functional hypogonadotropic hypogonadism that is associated with delayed but spontaneous pubertal development in the setting of an underlying condition or systemic illness, or permanent hypergonadotropic 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 hypogonadotropic 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 hypogonadotropic 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

Midline defects
- Septo-optic dysplasia
- Congenital hypopituitarism

Chemotherapy/radiation therapy
Trauma

Permanent hypergonadotropic 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)

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

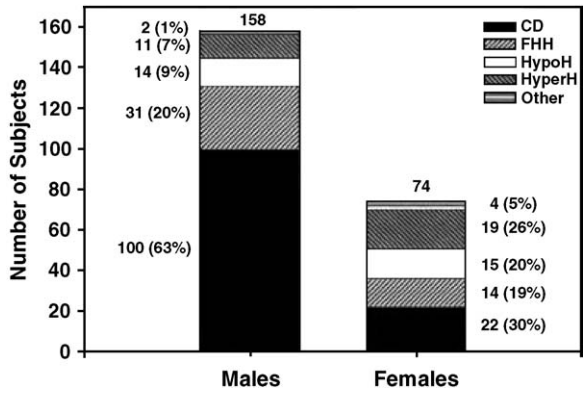

Fig. 2. Distribution of diagnostic categories in males and females with delayed puberty. CD, constitutional delay of growth and maturation; FHH, functional hypogonadotropic hypogonadism; HypoH, permanent hypogonadotropic hypogonadism; HyperH, permanent hypergonadotropic hypogonadism. (*From* Palmert MR, Malin HV, Boepple PA. Unsustained or slowly progressive puberty in young girls: initial presentation and long-term follow-up of 20 untreated patients. J Clin Endocrinol Metab 1999;84(2):415–23; with permission.)

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 17-α-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

Box 4. Evaluation of delayed puberty

Common initial screening tests
Careful history, physical exam, and assessment of growth velocity
Bone age
LH, FSH
Testosterone, estradiol
TSH, T4
Complete blood count
Sedimentation rate/C-reactive protein
Electrolytes, renal function
Liver enzymes
IGF-1, IGFBP-3
Urinalysis

Secondary tests to consider
Inflammatory bowel disease panel
Celiac disease panel
Prolactin
Karyotype
Head MRI
Pelvic ultrasound
LH levels following GnRH agonist

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 hypergonadotropic hypogonadism

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

[1] Apter D, Butzow TL, Laughlin GA, et al. Gonadotropin-releasing hormone pulse generator activity during pubertal transition in girls: pulsatile and diurnal patterns of circulating gonadotropins. J Clin Endocrinol Metab 1993;76(4):940–9.
[2] Wu FC, Butler GE, Kelnar CJ, et al. Ontogeny of pulsatile gonadotropin-releasing hormone secretion from midchildhood, through puberty, to adulthood in the human male: a study using deconvolution analysis and an ultrasensitive immunofluorometric assay. J Clin Endocrinol Metab 1996;81(5):1798–805.
[3] Ibanez L, Dimartino-Nardi J, Potau N, et al. Premature adrenarche—normal variant or forerunner of adult disease? Endocr Rev 2000;21(6):671–96.
[4] Auchus RJ, Rainey WE. Adrenarche - physiology, biochemistry and human disease. Clin Endocrinol 2004;60(3):288–96.
[5] Palmert MR, Hayden DL, Mansfield MJ, et al. The longitudinal study of adrenal maturation during gonadal suppression: evidence that adrenarche is a gradual process. J Clin Endocrinol Metab 2001;86(9):4536–42.
[6] Sklar CA, Kaplan SL, Grumbach MM. Evidence for dissociation between adrenarche and gonadarche: studies in patients with idiopathic precocious puberty, gonadal dysgenesis,

isolated gonadotropin deficiency, and constitutionally delayed growth and adolescence. J Clin Endocrinol Metab 1980;51(3):548–56.
[7] Ilondo MM, Vanderschueren-Lodeweyckx M, Vlietinck R, et al. Plasma androgens in children and adolescents. Part II. A longitudinal study in patients with hypopituitarism. Horm Res 1982;16(2):78–95.
[8] Wierman ME, Beardsworth DE, Crawford JD, et al. Adrenarche and skeletal maturation during luteinizing hormone releasing hormone analogue suppression of gonadarche. J Clin Invest 1986;77(1):121–6.
[9] Remer T, Manz F. Role of nutritional status in the regulation of adrenarche. J Clin Endocrinol Metab 1999;84(11):3936–44.
[10] Ong KK, Potau N, Petry CJ, et al. Opposing influences of prenatal and postnatal weight gain on adrenarche in normal boys and girls. J Clin Endocrinol Metab 2004;89(6): 2647–51.
[11] Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44(235):291–303.
[12] Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45(239):13–23.
[13] Lee PA. Normal ages of pubertal events among American males and females. J Adolesc Health Care 1980;1(1):26–9.
[14] Harlan WR, Grillo GP, Cornoni-Huntley J, et al. Secondary sex characteristics of boys 12 to 17 years of age: the US Health Examination Survey. J Pediatr 1979;95(2):293–7.
[15] Harlan WR, Harlan EA, Grillo GP. Secondary sex characteristics of girls 12 to 17 years of age: the US Health Examination Survey. J Pediatr 1980;96(6):1074–8.
[16] Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. N Engl J Med 1982; 306(17):1033–5.
[17] Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997;99(4):505–12.
[18] Kaplowitz PB, Oberfield SE. Re-examination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. Pediatrics 1999;104:936–41.
[19] Reiter EO, Lee PA. Have the onset and tempo of puberty changed? Arch Pediatr Adolesc Med 2001;155(9):988–9.
[20] Rosenfield RL, Bachrach LK, Chernausek SD, et al. Current age of onset of puberty. Pediatrics 2000;106(3):622–3.
[21] Finlay F, Jones R. Precocious puberty. Pediatrics 2000;106(1 Pt 1):162–3.
[22] Pathomvanich A, Merke DP, Chrousos GP. Early puberty: a cautionary tale. Pediatrics 2000;105(1 Pt 1):115–6.
[23] Lee PA, Kulin HE, Guo SS. Age of puberty among girls and the diagnosis of precocious puberty. Pediatrics 2001;107(6):1493.
[24] Emans SJ, Biro F. Secondary sexual characteristics and menses in young girls. Pediatrics 1998;101(5):949–50.
[25] Herman-Giddens ME, Kaplowitz PB, Wasserman R. Navigating the recent articles on girls' puberty in Pediatrics: what do we know and where do we go from here? Pediatrics 2004;113(4):911–7.
[26] Kaplowitz PB, Slora EJ, Wasserman RC, et al. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics 2001;108(2):347–53.
[27] Herman-Giddens ME, Bourdony C, Slora E, et al. Early puberty: a cautionary tale. Pediatrics 2001;107(3):609–10.
[28] Sun SS, Schubert CM, Chumlea WC, et al. National estimates of the timing of sexual maturation and racial differences among US children. Pediatrics 2002;110(5):911–9.

[29] Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988–1994. Pediatrics 2002;110(4):752–7.
[30] Marti-Henneberg C, Vizmanos B. The duration of puberty in girls is related to the timing of its onset. J Pediatr 1997;131(4):618–21.
[31] Grunt JA, Midyett LK, Simon SD, et al. When should cranial magnetic resonance imaging be used in girls with early sexual development? J Pediatr Endocrinol Metab 2004;17(5): 775–80.
[32] Chalumeau M, Hadjiathanasiou CG, Ng SM, et al. Selecting girls with precocious puberty for brain imaging: validation of European evidence-based diagnosis rule. J Pediatr 2003; 143(4):445–50.
[33] Midyett LK, Moore WV, Jacobson JD. Are pubertal changes in girls before age 8 benign? Pediatrics 2003;111(1):47–51.
[34] Stanhope R. Gonadotrophin-dependent precocious puberty and occult intracranial tumors: which girls should have neuro-imaging? J Pediatr 2003;143(4):426–7.
[35] Ng SM, Kumar Y, Cody D, et al. Cranial MRI scans are indicated in all girls with central precocious puberty. Arch Dis Child 2003;88(5):414–8.
[36] Herman-Giddens ME, Wang L, Koch G. Secondary sexual characteristics in boys: estimates from the national health and nutrition examination survey III, 1988–1994. Arch Pediatr Adolesc Med 2001;155(9):1022–8.
[37] Lee PA, Guo SS, Kulin HE. Age of puberty: data from the United States of America. Acta Pathol Microbiol Scand 2001;109(2):81–8.
[38] Biro FM, Lucky AW, Huster GA, et al. Pubertal staging in boys. J Pediatr 1995;127(1): 100–2.
[39] Parent AS, Teilmann G, Juul A, et al. The Timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev 2003;24(5):668–93.
[40] Palmert MR, Hirschhorn JN. Genetic approaches to stature, pubertal timing, and other complex traits. Mol Genet Metab 2003;80:1–10.
[41] Plant TM, Barker-Gibb ML. Neurobiological mechanisms of puberty in higher primates. Hum Reprod Update 2004;10(1):67–77.
[42] Ritzen EM. Early puberty: what is normal and when is treatment indicated? Horm Res 2003;60(Suppl 3):31–4.
[43] Kalantaridou SN, Chrousos GP. Clinical review 148: monogenic disorders of puberty. J Clin Endocrinol Metab 2002;87(6):2481–94.
[44] Cohen LE, Radovick S. Molecular basis of combined pituitary hormone deficiencies. Endocr Rev 2002;23(4):431–42.
[45] Achermann JC, Ozisik G, Meeks JJ, et al. Genetic causes of human reproductive disease. J Clin Endocrinol Metab 2002;87(6):2447–54.
[46] Dode C, Levilliers J, Dupont JM, et al. Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann's syndrome. Nat Genet 2003;33(4):463–5.
[47] Mantzoros CS, Flier JS, Rogol AD. A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. V. Rising leptin levels may signal the onset of puberty. J Clin Endocrinol Metab 1997;82(4):1066–70.
[48] De Roux N, Genin E, Carel JC, et al. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci U S A 2003; 100(19):10972–6.
[49] Seminara SB, Messager S, Chatzidaki EE, et al. The GPR54 gene as a regulator of puberty. N Engl J Med 2003;349(17):1614–27.
[50] Mitsushima D, Hei DL, Terasawa E. γ-Aminobutyric acid is an inhibitory neurotransmitter restricting the release of luteinizing hormone-releasing hormone before the onset of puberty. Proc Natl Acad Sci U S A 1994;91(1):395–9.

[51] Rivera C, Voipio J, Payne JA, et al. The K+/Cl- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. Nature 1999;397(6716):251–5.
[52] El Majdoubi M, Sahu A, Ramaswamy S, et al. Neuropeptide Y: a hypothalamic brake restraining the onset of puberty in primates. Proc Natl Acad Sci U S A 2000;97(11): 6179–84.
[53] Terasawa E, Fernandez DL. Neurobiological mechanisms of the onset of puberty in primates. Endocr Rev 2001;22(1):111–51.
[54] Prevot V, Rio C, Cho GJ, et al. Normal female sexual development requires neuregulin-erbB receptor signaling in hypothalamic astrocytes. J Neurosci 2003;23(1):230–9.
[55] Gottsch ML, Clifton DK, Steiner RA. Galanin-like peptide as a link in the integration of metabolism and reproduction. Trends Endocrinol Metab 2004;15(5):215–21.
[56] Gottsch ML, Cunningham MJ, Smith JT, et al. A role for kisspeptins in the regulation of gonadotropin secretion in the mouse. Endocrinology 2004;145(9):4073–7.
[57] Ojeda SR, Prevot V, Heger S, et al. Glia-to-neuron signaling and the neuroendocrine control of female puberty. Ann Med 2003;35(4):244–55.
[58] Biro FM, McMahon RP, Striegel-Moore R, et al. Impact of timing of pubertal maturation on growth in black and white female adolescents: the National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr 2001;138(5):636–43.
[59] Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics 2002;110(5):903–10.
[60] Gore AC. Environmental toxicant effects on neuroendocrine function. Endocrine 2001; 14(2):235–46.
[61] Colon I, Caro D, Bourdony CJ, et al. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ Health Perspect 2000;108(9):895–900.
[62] Tiwary CM. Premature sexual development in children following the use of estrogen- or placenta-containing hair products. Clin Pediatr 1998;37(12):733–9.
[63] Setchell KD, Zimmer-Nechemias L, Cai J, et al. Exposure of infants to phyto-oestrogens from soy-based infant formula. Lancet 1997;350(9070):23–7.
[64] Greim HA. The endocrine and reproductive system: adverse effects of hormonally active substances? Pediatrics 2004;113(Suppl 4):1070–5.
[65] Kaplowitz P. Clinical characteristics of 104 children referred for evaluation of precocious puberty. J Clin Endocrinol Metab 2004;89(8):3644–50.
[66] Bridges NA, Christopher JA, Hindmarsh PC, et al. Sexual precocity: sex incidence and aetiology. Arch Dis Child 1994;70(2):116–8.
[67] Cisternino M, Arrigo T, Pasquino AM, et al. Etiology and age incidence of precocious puberty in girls: a multicentric study. J Pediatr Endocrinol Metab 2000;13(Suppl 1): 695–701.
[68] De Sanctis V, Corrias A, Rizzo V, et al. Etiology of central precocious puberty in males: the results of the Italian Study Group for Physiopathology of Puberty. J Pediatr Endocrinol Metab 2000;13(Suppl 1):687–93.
[69] Klein KO, Mericq V, Brown-Dawson JM, et al. Estrogen levels in girls with premature thelarche compared with normal prepubertal girls as determined by an ultrasensitive recombinant cell bioassay. J Pediatr 1999;134(2):190–2.
[70] Pescovitz OH, Hench KD, Barnes KM, et al. Premature thelarche and central precocious puberty: the relationship between clinical presentation and the gonadotropin response to luteinizing hormone-releasing hormone. J Clin Endocrinol Metab 1988;67(3):474–9.
[71] Pasquino AM, Pucarelli I, Passeri F, et al. Progression of premature thelarche to central precocious puberty. J Pediatr 1995;126(1):11–4.
[72] Ibanez L, Potau N, Zampolli M, et al. Hyperinsulinemia in postpubertal girls with a history of premature pubarche and functional ovarian hyperandrogenism. J Clin Endocrinol Metab 1996;81(3):1237–43.

[73] Palmert MR, Malin HV, Boepple PA. Unsustained or slowly progressive puberty in young girls: initial presentation and long-term follow-up of 20 untreated patients. J Clin Endocrinol Metab 1999;84(2):415–23.
[74] Roman R, Johnson MC, Codner E, et al. Activating GNAS1 gene mutations in patients with premature thelarche. J Pediatr 2004;145(2):218–22.
[75] Neely EK, Wilson DM, Lee PA, et al. Spontaneous serum gonadotropin concentrations in the evaluation of precocious puberty. J Pediatr 1995;127(1):47–52.
[76] Ikegami S, Moriwake T, Tanaka H, et al. An ultrasensitive assay revealed age-related changes in serum oestradiol at low concentrations in both sexes from infancy to puberty. Clin Endocrinol 2001;55(6):789–95.
[77] Herter LD, Golendziner E, Flores JA, et al. Ovarian and uterine findings in pelvic sonography: comparison between prepubertal girls, girls with isolated thelarche, and girls with central precocious puberty. J Ultrasound Med 2002;21(11):1237–46.
[78] Rosenfield RL, Garibaldi LR, Moll GW Jr, et al. The rapid ovarian secretory response to pituitary stimulation by the gonadotropin-releasing hormone agonist nafarelin in sexual precocity. J Clin Endocrinol Metab 1986;63(6):1386–9.
[79] Ibanez L, Potau N, Zampolli M, et al. Use of leuprolide acetate response patterns in the early diagnosis of pubertal disorders: comparison with the gonadotropin-releasing hormone test. J Clin Endocrinol Metab 1994;78(1):30–5.
[80] Eckert KL, Wilson DM, Bachrach LK, et al. A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. Pediatrics 1996;97(4):517–9.
[81] Brito VN, Latronico AC, Arnhold IJ, et al. A single luteinizing hormone determination 2 hours after depot leuprolide is useful for therapy monitoring of gonadotropin-dependent precocious puberty in girls. J Clin Endocrinol Metab 2004;89(9):4338–42.
[82] Bar A, Linder B, Sobel EH, et al. Bayley-Pinneau method of height prediction in girls with central precocious puberty: correlation with adult height. J Pediatr 1995;126(6):955–8.
[83] Weise M, Flor A, Barnes KM, et al. Determinants of growth during gonadotropin-releasing hormone analog therapy for precocious puberty. J Clin Endocrinol Metab 2004;89(1): 103–7.
[84] Ehrhardt AA, Meyer-Bahlburg HF. Psychosocial aspects of precocious puberty. Horm Res 1994;41(Suppl 2):30–5.
[85] Graber JA, Seeley JR, Brooks-Gunn J, et al. Is pubertal timing associated with psychopathology in young adulthood. J Am Acad Child Adolesc Psychiatry 2004;43(6): 718–26.
[86] Klein KO. Precocious puberty: who has it? Who should be treated? J Clin Endocrinol Metab 1999;84(2):411–4.
[87] Carel JC, Lahlou N, Jaramillo O, et al. Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). J Clin Endocrinol Metab 2002;87(9):4111–6.
[88] Trueman JA, Tillmann V, Cusick CF, et al. Suppression of puberty with long-acting goserelin (Zoladex-LA): effect on gonadotrophin response to GnRH in the first treatment cycle. Clin Endocrinol 2002;57(2):223–30.
[89] Partsch CJ, Heger S, Sippell WG. Management and outcome of central precocious puberty. Clin Endocrinol 2002;56(2):129–48.
[90] Carel JC, Lahlou N, Roger M, et al. Precocious puberty and statural growth. Hum Reprod Update 2004;10(2):135–47.
[91] van der Sluis IM, Boot AM, Krenning EP, et al. Longitudinal follow-up of bone density and body composition in children with precocious or early puberty before, during and after cessation of GnRH agonist therapy. J Clin Endocrinol Metab 2002;87(2):506–12.
[92] Palmert MR, Mansfield MJ, Crowley WF Jr, et al. Is obesity an outcome of gonadotropin-releasing hormone agonist administration? Analysis of growth and body composition in 110 patients with central precocious puberty. J Clin Endocrinol Metab 1999;84(12):4480–8.

[93] Bhatia S, Neely EK, Wilson DM. Serum luteinizing hormone rises within minutes after depot leuprolide injection: implications for monitoring therapy. Pediatrics 2002;109(2): E30.
[94] Eugster EA, Rubin SD, Reiter EO, et al. Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multi-center trial. J Pediatr 2003;143(1):60–6.
[95] Sedlmeyer IL, Palmert MR. Delayed puberty: analysis of a large case series from an academic center. J Clin Endocrinol Metab 2002;87(4):1613–20.
[96] Rosenfield RL. Clinical review 6: diagnosis and management of delayed puberty. J Clin Endocrinol Metab 1990;70(3):559–62.
[97] Gill MS, Hall CM, Tillmann V, et al. Constitutional delay in growth and puberty (CDGP) is associated with hypoleptinaemia. Clin Endocrinol 1999;50(6):721–6.
[98] Kaplowitz P. Delayed puberty in obese boys: comparison with constitutional delayed puberty and response to testosterone therapy. J Pediatr 1998;133(6):745–9.
[99] Sedlmeyer IL, Hirschhorn JN, Palmert MR. Pedigree analysis of constitutional delay of growth and maturation: determination of familial aggregation and inheritance patterns. J Clin Endocrinol Metab 2002;87(12):5581–6.
[100] Snieder H, MacGregor AJ, Spector TD. Genes control the cessation of a woman's reproductive life: a twin study of hysterectomy and age at menopause. J Clin Endocrinol Metab 1998;83(6):1875–80.
[101] de Vries L, Kauschansky A, Shohat M, et al. Familial central precocious puberty suggests autosomal-dominant inheritance. J Clin Endocrinol Metab 2004;89(4):1794–800.
[102] Crowne EC, Shalet SM, Wallace WH, et al. Final height in boys with untreated constitutional delay in growth and puberty. Arch Dis Child 1990;65(10):1109–12.
[103] LaFranchi S, Hanna CE, Mandel SH. Constitutional delay of growth: expected versus final adult height. Pediatrics 1991;87(1):82–7.
[104] Albanese A, Stanhope R. Predictive factors in the determination of final height in boys with constitutional delay of growth and puberty. J Pediatr 1995;126(4):545–50.
[105] Albertsson-Wikland K, Rosberg S. Analyses of 24-hour growth hormone profiles in children: relation to growth. J Clin Endocrinol Metab 1988;67(3):493–500.
[106] Racine MS, Symons KV, Foster CM, et al. Augmentation of growth hormone secretion after testosterone treatment in boys with constitutional delay of growth and adolescence: evidence against an increase in hypothalamic secretion of growth hormone-releasing hormone. J Clin Endocrinol Metab 2004;89(7):3326–31.
[107] Finkelstein JS, Neer RM, Biller BM, et al. Osteopenia in men with a history of delayed puberty. N Engl J Med 1992;326(9):600–4.
[108] Bertelloni S, Baroncelli GI, Ferdeghini M, et al. Normal volumetric bone mineral density and bone turnover in young men with histories of constitutional delay of puberty. J Clin Endocrinol Metab 1998;83(12):4280–3.
[109] Yap F, Hogler W, Briody J, et al. The skeletal phenotype of men with previous constitutional delay of puberty. J Clin Endocrinol Metab 2004;89(9):4306–11.
[110] Lee PD, Rosenfeld RG. Psychosocial correlates of short stature and delayed puberty. Pediatr Clin North Am 1987;34(4):851–63.
[111] Arrigo T, Rulli I, Sferlazzas C, et al. Pubertal development in cystic fibrosis: an overview. J Pediatr Endocrinol Metab 2003;16(Suppl 2):267–70.
[112] Johannesson M, Gottlieb C, Hjelte L. Delayed puberty in girls with cystic fibrosis despite good clinical status. Pediatrics 1997;99(1):29–34.
[113] Weyler RT, Yurko-Mauro KA, Rubenstein R, et al. CFTR is functionally active in GnRH-expressing GT1–7 hypothalamic neurons. Am J Physiol 1999;277:C563–71.
[114] Ghai K, Cara JF, Rosenfield RL. Gonadotropin releasing hormone agonist (nafarelin) test to differentiate gonadotropin deficiency from constitutionally delayed puberty in teen-age boys—a clinical research center study. J Clin Endocrinol Metab 1995;80(10):2980–6.
[115] Zamboni G, Antoniazzi F, Tato L. Use of the gonadotropin-releasing hormone agonist triptorelin in the diagnosis of delayed puberty in boys. J Pediatr 1995;126:756–8.

[116] Kauschansky A, Dickerman Z, Phillip M, et al. Use of GnRH agonist and human chorionic gonadotrophin tests for differentiating constitutional delayed puberty from gonadotrophin deficiency in boys. Clin Endocrinol 2002;56(5):603–7.
[117] Wilson DM, Kei J, Hintz RL, et al. Effects of testosterone therapy for pubertal delay. Am J Dis Child 1988;142(1):96–9.
[118] Richman RA, Kirsch LR. Testosterone treatment in adolescent boys with constitutional delay in growth and development. N Engl J Med 1988;319(24):1563–7.
[119] Wilson DM, McCauley E, Brown DR, et al. Oxandrolone therapy in constitutionally delayed growth and puberty. Bio-Technology General Corporation Cooperative Study Group. Pediatrics 1995;96(6):1095–100.
[120] Crowne EC, Wallace WH, Moore C, et al. Degree of activation of the pituitary-testicular axis in early pubertal boys with constitutional delay of growth and puberty determines the growth response to treatment with testosterone or oxandrolone. J Clin Endocrinol Metab 1995;80(6):1869–75.
[121] Tse WY, Buyukgebiz A, Hindmarsh PC, et al. Long-term outcome of oxandrolone treatment in boys with constitutional delay of growth and puberty. J Pediatr 1990;117(4): 588–91.
[122] Franklin SL, Geffner ME. Precocious puberty secondary to topical testosterone exposure. J Pediatr Endocrinol Metab 2003;16(1):107–10.
[123] Kunz GJ, Klein KO, Clemons RD, et al. Virilization of young children after topical androgen use by their parents. Pediatrics 2004;114(1):282–4.
[124] Wickman S, Sipila I, Ankarberg-Lindgren C, et al. A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomised controlled trial. Lancet 2001;357(9270):1743–8.
[125] Wickman S, Kajantie E, Dunkel L. Effects of suppression of estrogen action by the p450 aromatase inhibitor letrozole on bone mineral density and bone turnover in pubertal boys. J Clin Endocrinol Metab 2003;88(8):3785–93.
[126] Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet 2003; 362(9382):428–32.
[127] Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291(14):1701–12.
[128] Ankarberg-Lindgren C, Elfving M, Wikland KA, et al. Nocturnal application of transdermal estradiol patches produces levels of estradiol that mimic those seen at the onset of spontaneous puberty in girls. J Clin Endocrinol Metab 2001;86(7):3039–44.
[129] Piippo S, Lenko H, Kainulainen P, et al. Use of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome. J Clin Endocrinol Metab 2004;89(7):3241–7.