Treatment and Outcomes of Precocious Puberty: An Update

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Precocious puberty is a common problem affecting up to 29 per 100 000 girls per year. The earliest identified neuroendocrine change in early puberty thus far is increased kisspeptin secretion from the arcuate nucleus and the anteroventric paraventricular nucleus of the hypothalamus. The regulation of kisspeptin secretion is not well understood, but neurokinin B and dynorphin provide autocrine regulation. The etiologies of precocious puberty may be subdivided into GnRH-dependent and GnRH-independent causes. GnRH-dependent precocious puberty, often called central precocious puberty (CPP), is usually treated with GnRH analogs. Newer developments in the treatment of CPP include expanded data on the safety and efficacy of the subdermal histrelin implant, which is useful for long-term treatment, although removal may be difficult in some cases. Preliminary data suggest that the implant may be left in place for up to 2 years without loss of biochemical suppression. In the last 2 years, more data have been published concerning extended-release leuprolide acetate injections that indicate that the 11.25-mg dose may not provide full biochemical suppression but may clinically suppress signs of puberty, including the accelerated growth velocity and advanced skeletal maturation seen in CPP. Treatment options for familial male-limited precocious puberty and McCune-Albright syndrome are expanding as well, although data are preliminary. Long-term outcome studies of CPP indicate overall good menstrual and reproductive function, but the prevalence of polycystic ovary syndrome may be higher than in the general population. Remarkably few studies have evaluated the behavioral and psychological outcomes of precocious puberty, in contrast to early normal maturation. Additional outcome studies of endocrine, metabolic, and psychological effects of CPP are clearly needed. (*J Clin Endocrinol Metab* 98: 2198–2207, 2013)

Precocious puberty is one of the more common conditions encountered in pediatric endocrinology practice. New articles about increasingly early pubertal development have appeared in the lay press, making families' questions about their children's pubertal development increasingly common. Over the last 2 years, new information has become available, particularly related to therapies and outcomes, making an update in this field timely.

Precocious puberty can be defined as sex hormone production or exposure occurring earlier than the norms for gender and racial or ethnic background. Just how common is precocious puberty? On the basis of a population-based registry, the prevalence of all forms of precocious puberty in Denmark has been estimated as 0.2% of girls and < 0.05% of boys. The annual incidence of precocious puberty in girls varied over an 8-year period from 15–29 per 100 000 girls. The incidence in boys was approximately 10- to 15-fold lower (1). These figures include those with the variants of premature thelarche (PT), premature adrenarche (PA), and early normal maturing children in addition to those with true central precocious puberty (CPP), which made up 46%. More recently, estimates from a broad hospital-based registry in Spain put the annual incidence of CPP in girls at 1.1 per 100 000 (2). Although this seems much lower than the Danish study, there were significant methodological differences, including restricting data collection to tertiary care centers with pediatric endocrinology services, inclusion of only

Abbreviations: ARC, arcuate nucleus; BMI, body mass index; CNS, central nervous system; CPP, central precocious puberty; FMPP, familial male-limited precocious puberty; GnRHa, GnRH analog(s); KNDy, Kisspeptin, Neurokinin B, Dynorphin; MAS, McCune-Albright syndrome; PA, premature adrenarche; PCOS, polycystic ovary syndrome; PPP, peripheral precocious puberty; PT, premature thelarche.

those with CPP, and a more stringent definition of precocious puberty.

This paper will briefly review the changes typically seen during pubertal development in normal children and some of the neuroendocrine mechanisms regulating this process. Just how early is too early for puberty has been the subject of much debate. Space constraints prevent a detailed discussion of this controversy, but some recent articles will be reviewed. The focus will then shift to precocious puberty, with an emphasis on recent progress in its treatment and our understanding about outcomes.

Normal Puberty

Physical changes

Normal puberty in girls usually begins with thelarche (the onset of breast buds), followed within a few months by pubarche (the onset of pubic hair). Pubarche is usually caused by secretion of adrenal androgens, the initiation of which is termed adrenarche. In boys, the first sign of pubertal development is usually testicular enlargement. In both sexes, however, pubic hair may be the first manifestation of puberty (3). The term "gonadarche" is often used to indicate the initiation of sex hormone production from the ovary or testis. The degree of pubertal maturation is usually described using the Tanner stages of sexual maturation (4) (Table 1). Over the ensuing years, these maturational changes progress, and in girls, menarche usually occurs during Tanner stage 4 breast development. In males, testicular volume increases from 1–3 mL before puberty up to 15–25 mL in adulthood. In most adolescents, maturation is complete by 4 years after its initiation.

Endocrine changes

In the prepubertal child, GnRH is released in low amplitude pulses at a relatively low frequency. The earliest identified neuroendocrine manifestation of puberty is the production of kisspeptin from hypothalamic neurons. Kisspeptin alters release of GnRH from the hypothalamus. In the early stages of puberty, GnRH pulse amplitude increases and pulse frequency increases to every 1–2 hours, primarily at night (5). As maturation progresses, these changes extend into the daytime hours. In response to GnRH secretion, LH and FSH production also increase, initially during the night and then during the day in later pubertal stages.

In the female, FSH promotes early follicular development in the ovary, and in conjunction with LH leads to gradually increasing estradiol secretion. Estradiol concentrations in early puberty are quite low and vary with time of day, with peak levels occurring in the morning hours. Estradiol is maintained at higher levels throughout the day as puberty progresses, and overall concentrations gradually increase with progressing puberty. In the male, increasing LH production in the nighttime hours results in T secretion, with peak levels occurring in the early morning. Although daytime T concentrations increase with progression of puberty, there continues to be a diurnal variation in T levels into young adulthood. Serum concentrations of T increase from <10 ng/dL before puberty to 300–900 ng/dL in adulthood, with the most rapid rise occurring between male genital Tanner stages 2 and 3.

At the low concentrations seen in early puberty, virtually all commercial assays for T and estradiol suffer from inadequate sensitivity and excessively high coefficients of

Table 1. Tanner Stages of Pubertal Maturation

Stage	Breast	Pubic Hair in Males and Females	Male Genitalia
1	Prepubertal	Prepubertal	Prepubertal
2	Breast budding, elevation of both breast and nipple as a small mound	Sparse growth of long, lightly pigmented hairs at the base of the penis in males or the mons veneris/labia majora in females	Enlargement of the testes and scrotum, thinning and reddening of the scrotal skin, penis remains prepubertal
3	Continued enlargement of both breast and areola without separation of their contours	Additional darkening and coarsening of hair, spreading over the pubic symphysis	Further growth of testes and scrotum, enlargement of the penis in length
4	The areola and nipple form a secondary mound projecting above the contour of the breast	Adult in character but confined to the suprapubic area in males and females	Further growth of testes and scrotum with pigmentation of the scrotal skin, further enlargement of the penis in width, with maturation of the glans
5	Adult shape, areola and nipple recessed to the contour of the breast	Adult in distribution with spread to the medial thighs in males and females. May extend to the lower abdomen in males.	Testes, scrotum, and penis are adult in size and shape

variation. This makes measurement of sex steroid levels in children fraught with difficulty. A consortium of stakeholder organizations has efforts under way to improve the performance of sex steroid assays.

Regulation of normal puberty

The discovery of kisspeptin and its receptor has led to expanded understanding of the regulation of normal puberty over the last 10 years. Although it is known that kisspeptin promotes GnRH secretion, the untangling of the many inputs controlling kisspeptin production is ongoing. Kisspeptin-producing hypothalamic neurons in the arcuate nucleus (ARC) and anteroventral periventricular area coproduce neurokinin B and dynorphin, which respectively appear to have local stimulatory and repressive actions on kisspeptin release and are thus known as KNDy (Kisspeptin, Neurokinin B, Dynorphin) neurons (6). This overlapping autocrine feedback allows for fine control of kisspeptin secretion. Additionally, KNDy neurons may be a site of action for the negative feedback effects of estradiol (7), and decreases in the intensity of this negative feedback occur as puberty begins. In reproductively mature females, regulation of hypothalamic reproductive capacity is influenced by the energy status of the organism, with peripheral energy stores being signaled to the brain by leptin and ghrelin. Leptin, produced in adipose tissue and directly related to stored energy, acts through its receptor to stimulate kisspeptin secretion in the ARC, although it is unclear whether this is a direct action on KNDy neurons or whether leptin acts via an intermediate cell (8). Ghrelin secretion varies over the short term with food intake but also is influenced in the long term by energy stores. Ghrelin appears to suppress kisspeptin secretion in the ARC and anteroventral periventricular area. Additional signals of energy balance that may influence kisspeptin secretion include neuropeptide Y and proopiomelanocortin. These mechanisms are important for maintenance of ovarian function, but their role in the initiation of puberty is not known, although they are thought to be permissive. Virtually all in vivo studies of this system have been performed in rodents and other mammals, including nonhuman primates (reviewed in Ref. 9). Activating mutations of the genes for kisspeptin and its receptor have been found in individuals with precocious puberty (10, 11). Although mutations of neurokinin b and dynorphin could theoretically cause early pubertal development, such mutations have not yet been identified (12).

A large body of evidence implicates hypothalamic astrocytes and other neuroglial cells in the regulation of puberty and reproductive function (reviewed in Ref. 13). Neuroglial cells influence GnRH neurons in at least 2 ways. Hypothalamic astrocytes secrete a host of growth factors, such as TGF-β, basic fibroblast growth factor, and epidermal growth factor-like peptides. These growth factors act via specific receptors on GnRH neurons to increase neuronal growth and function. Additionally, glial cells are directly apposed to GnRH neurons in a dynamic fashion, and increases in levels of apposition are associated with greater GnRH secretion. The apposition is negatively influenced by estradiol, and this may be a mechanism by which negative feedback occurs. Collections of neuroglial cells forming hypothalamic hamartomas are commonly associated with precocious puberty. Although this form of precocious puberty has been attributed to an ectopic source of GnRH pulsatility within the hamartoma, there is evidence that neuroglial effects on hypothalamic GnRH neurons may play a role (14).

There has been a great deal of controversy over the issue of timing of puberty. This has been extensively reviewed elsewhere (15). Although 8 years was the traditionally accepted lower limit of normal for thelarche and pubarche in girls and the average age at thelarche was commonly believed to be 10.5 years, this was called into question in the late 1990s. The lower limit of 8 years came from studies published in the 1950s and 1960s of children evaluated between 1930 and 1970. These included lower socioeconomic status white children in the United Kingdom and higher socioeconomic status children in Ohio and California. More recent data from the early 1990s, however, indicated that breast development was present in 15% of African American girls and 5% of white girls at age 7 years. The average age at thelarche was 10 years for white girls and 8.9 years for African American girls (16). These findings were later confirmed in the National Health and Nutrition Examination Survey (NHANES) III dataset. More recently, data from the Breast Cancer and Environmental Research Centers collected from sites in New York, Cincinnati, and San Francisco indicated that between their seventh and eighth birthdays, 10% of white girls, 23% of African American girls, and 15% of Hispanic girls had breast development of at least Tanner stage 2 (17). The National Institute of Child Health and Human Development (NICHD)-sponsored Study of Early Child Care and Youth Development was a longitudinal study of children at 10 university centers across the United States started in 1990. Girls followed annually from birth demonstrated an average age at breast Tanner stage 2 of 9.9 years for white girls and 9.1 years for African American girls (3). Although these reports indicate that Tanner stage 2 breast development in girls occurs earlier than previously reported, the ages at Tanner stage 3 are similar to older data. In contrast to the ages at thelarche, the timing of menarche is only minimally earlier, with most current studies documenting an average age between 12 and 12.5

years, only 4 months younger than documented in the mid-20th century.

In boys, similar data exist. The original studies documented an average age at initiation of puberty of 11.5 years, with onset before age 9 considered pathological. NHANES III data show an average age at genital Tanner stage 2 of 10.1 years for white boys and 9.5 years for African American boys. This was confirmed in 2 recent studies. In the NICHD study discussed above, boys entered genital Tanner stage 2 at a mean age of 10.4 years for whites and 9.6 years for African Americans (3). Similar findings were recently published from the American Academy of Pediatrics' Pediatric Research in Office Settings (PROS) network in a cross-sectional study. These investigators found an average age at genital Tanner stage 2 of 10.1 years in whites and 9.1 years in African Americans (18).

Concerns about the validity of these studies have included the establishment of breast Tanner stage by visual inspection rather than palpation of breast buds. However, the NICHD study included breast palpation, and analysis of a subset of subjects in the PROS study that had both visual inspection and palpation demonstrated similar findings. In boys, genital Tanner staging is subjective and thus may not reflect the actual developmental status. The presence of pubic hair may be a more objective finding than genital development, and both the NICHD and the PROS studies found younger ages at onset of pubic hair in boys than early studies.

The reasons for the discordance between early and more recent studies are not clear. Significant methodological differences include varying race/ethnicities, socioeconomic factors, definitions of the onset of puberty, data collection approaches, statistical analyses, and longitudinal vs cross-sectional observations. The worldwide increase in obesity in the last 20 years may be a factor, and indeed, studies have shown correlations between measures of body fat and timing of puberty, particularly in girls (18–21).

With a larger number of children entering puberty at an earlier age, it becomes important to distinguish the early-normal maturing patient from the one with pathologically precocious puberty (22). This requires a thoughtful evaluation of historical and physical examination findings, assessment of the rate of maturation, and hormonal measurements.

Precocious Puberty

Differential diagnosis

Causes of abnormally early pubertal maturation may be separated into GnRH-dependent and GnRH-independent processes. GnRH-dependent precocious puberty, often called central precocious puberty, results from activation of the hypothalamic-pituitary-gonadal axis by a variety of central nervous system (CNS) abnormalities (Table 2). The range of etiologies of CPP is similar in boys and girls, although idiopathic CPP is much more common in girls, comprising roughly 90% of cases. Boys with precocious puberty are much more likely to have identifiable pathology. Internationally adopted children appear to be at increased risk for CPP. The reason for this is unclear, but

Table 2. Etiologies of Precocious Puberty

GnRH-Dependent Females and Males	GnRH-Independent Females	GnRH-Independent Males
Idiopathic	MAS	FMPP
International adoption	Estrogen-secreting ovarian tumor	Leydig cell tumor
Acquired CNS insults	Ovarian cyst	Human chorionic gonadotropin-secreting tumor
Brain tumor [astrocytoma, pineal tumor, optic pathway glioma (NF1), craniopharyngioma (rare)]	Estrogen-secreting adrenal tumor	Androgen-secreting adrenal tumor
Cerebral palsy	Exogenous estrogen exposure	Exogenous T exposure
Hydrocephalus	Peutz-Jegher syndrome	Congenital adrenal hyperplasia
CNS irradiation	Primary hypothyroidism	Primary hypothyroidism (testicular enlargement only)
CNS trauma	Aromatase excess	Familial glucocorticoid resistance
CNS infection		MAS (rare)
CNS granulomatous disease		
Subarachnoid cyst		
Hypothalamic hamartoma		
Neurofibromatosis, type 1		
Tuberous sclerosis		
Sturge-Weber syndrome		
Withdrawal of chronic sex hormone exposure		
Septo-optic dysplasia (rare)		
Gain of function mutation of kisspeptin/kisspeptin receptor		

it is hypothesized that nutritional deprivation in early life followed by increased adiposity after adoption triggers the endocrine and physical changes of puberty earlier than would have otherwise occurred (2, 23). Genetic and other environmental factors may also play roles.

Unlike CPP, the etiologies of GnRH-independent peripheral precocious puberty (PPP) vary between boys and girls (Table 2). Causes of PPP include production of sex steroids by the gonad in an unregulated fashion, such as in McCune-Albright syndrome (MAS) or familial male-limited precocious puberty (FMPP); sex steroid secretion by extragonadal tissue, such as the adrenal gland as occurs in congenital adrenal hyperplasia; rare sex steroid or β-human chorionic gonadotropin-secreting tumors; or exposure to exogenous sex hormones. Long-term exposure to sex steroids due to GnRH-independent processes may result in early entry into central puberty through mechanisms that are not well understood. This effect usually occurs after withdrawal of the exposure, such as after initiation of treatment in a male with simple virilizing congenital adrenal hyperplasia or elimination of prolonged exogenous sex steroid exposure.

Two common variants of precocious puberty exist. Premature thelarche (PT) refers to the isolated development of breast tissue. Typically, there are no other pubertal findings, such as accelerated linear growth, rapid progression of breast development, or advanced skeletal maturation. Classic PT does not progress and usually regresses over several months. PT often occurs in toddler girls but may also be seen in older girls with isolated breast development. Premature adrenarche (PA) is a variant in which mildly elevated concentrations of adrenal-derived androgens cause gradually progressive pubic and/or axillary hair growth. Breast development is absent, and skeletal maturation may be mildly advanced. In some populations, PA has been associated with increased cardiometabolic risk factors and an increased risk for polycystic ovary syndrome (PCOS) in later life (24, 25). A syndrome of "premature menarche" has been described, but it is poorly defined and understood (26).

Diagnosis of precocious puberty

In the evaluation of a child with early pubertal maturation, distinguishing between the common variants of PT or PA and true precocious puberty is an important step. Isolated nonprogressive breast development in a girl, especially a toddler, may be simple PT. Girls with pubic hair and/or axillary hair and no breast development or boys with pubic/axillary hair and no testicular enlargement are likely to have PA. Findings that suggest pathology include a rapid tempo of progression; advanced development; rapid linear growth; advanced skeletal maturation; and in

girls, the presence of both breasts and pubic hair (27). Once pathological precocious puberty is established, the next step is determining whether the process is GnRH-dependent or -independent. Boys with CPP typically have symmetrically enlarged testicular volumes, whereas those with most forms of PPP have testes that are either prepubertal or disproportionately small compared with the degree of virilization. Rarely, boys with bilateral testicular Leydig cell or adrenal rest tumors are encountered. In girls, pelvic ultrasonography to assess ovarian volume is not sufficiently sensitive to distinguish the form of precocious puberty (28), but it may be helpful as an adjunct to other studies. Biochemical diagnostic criteria for CPP include a serum LH concentration > 5 U/L after GnRH or leuprolide administration or a basal LH > 0.3 U/L using ultrasensitive assays. In girls, a less commonly used criterion is a ratio of peak LH/peak FSH over 0.66 after GnRH stimulation (29).

Treatment

Central precocious puberty

Overview

The mainstay of treatment for CPP is GnRH analogs (GnRHa). This group of drugs provides constant serum levels of GnRH activity and thus overrides the pulsatility of endogenous GnRH. Although there are many different analogs with different routes of administration, the primary agent in the United States for many years was depot im injections of leuprolide acetate administered every 4 weeks. A recently published consensus statement from the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society (now the Pediatric Endocrine Society) highlighted that reasons for treatment include the preservation of adult height potential and psychosocial difficulties with early puberty and menarche (30). The issue of adult height preservation is particularly the case for girls under 6 years old, in whom studies have indicated the greatest increase in adult height with treatment. Those between 6 and 8 years form a more heterogeneous group. Some with very rapid or advanced puberty may benefit, although many have a slowly progressive form that yields a normal height outcome without treatment. There appears to be little utility to treating girls over age 8 for the purposes of increasing adult height.

Newer treatment agents

Histrelin implant

In the last 10 years, the GnRHa histrelin has been incorporated into a subdermal hydrogel implant. Although initially developed for treatment of prostate cancer, this

has found a role in suppression of CPP, although it is not available in all countries. The first report of a large-scale treatment study in 2007 included data on 36 subjects (33 girls) and found that stimulated LH concentrations declined quickly and suppression was maintained for 1 year (31). Bone age advancement improved during this interval. This led to the approval of the histrelin implant by the Food and Drug Administration that year. A subset of 31 subjects went on to have a second implant inserted after 1 year, and these subjects were followed for an additional year (32). Over the course of the first year, the mean serum estradiol concentration declined from 24.5 ± 22.7 to 5.9 ± 2.3 pg/mL in the treatment-naive group. Over the entire 2 years of the study, peak stimulated LH concentrations in treatment-naive girls declined from 28 U/L at study entry to 0.8 U/L at 1 year and then to 0.51 U/L after 2 years. In girls previously treated with depot leuprolide acetate injections, LH levels at study entry were lower (2.1 ± 2.2 U/L) but were similarly suppressed at 1 and 2 years. Over the course of the study, predicted adult height by the Bayley-Pinneau technique increased by 5.1 cm compared to baseline predictions. Minor adverse events, mainly pain and/or bruising at the insertion site, were seen in 61% of subjects. After 1 year in place, the implants became relatively brittle, and breakage of the device at removal was common, occurring in 16 and 22% of cases at 1 and 2 years, respectively. In 5–10% of removals, ultrasonography was required to locate fragments of the implant.

As currently produced, the histrelin implant contains sufficient medication to last for 2 years based on established release rates, raising the possibility of leaving a single implant in place for 2 years instead of 1 year. A recent study of 32 children treated for CPP with the histrelin implant has shown that this approach is potentially safe and effective. Preliminary results at 2 years in 18 of the 32 subjects have been presented (33). Peak LH levels were 1.0 U/L at 1 year and were unchanged at 2 years. Although 2 subjects had physical signs of pubertal progression, these individuals did not have any biochemical evidence of escape from suppression. The rate of skeletal maturation remained appropriately low over the 2-year period. Two-year findings in the full dataset are similar (Erica Eugster, personal communication, December 20, 2012). Larger prospective studies are required to confirm these observations.

A recent investigation of the time course of the hypothalamic-pituitary-gonadal axis recovery after histrelin implant removal showed that changes in free α-subunit serum concentrations occur rapidly. Unlike intact gonadotropins, free α-subunit levels paradoxically increase with GnRHa pubertal suppression (34). In a study of 10 girls treated with the histrelin implant, serum concentrations of free α-subunit declined within 1 week of implant removal from 1.02 ± 0.29 to 0.31 ± 0.12 ng/mL (normal, ≤ 0.6 for prepubertal girls) (35). Unstimulated serum LH and FSH levels demonstrated a statistically significant increase by 3 weeks after removal, and higher estradiol levels were noted by 6 weeks. Interestingly, the lack of decline in free α-subunit levels was able to identify a subject who had residual implant fragments after breakage of the implant at removal. After eventual localization and removal of the fragments, free α-subunit levels decreased to normal.

In patients treated with depot leuprolide acetate, sterile abscesses have been reported in 1.5–3% of patients, thought to be due to reactions to the polymers used to convey slower drug release. Sterile abscess has also been reported during the use of the histrelin implant (36).

Extended depot leuprolide acetate

Depot leuprolide acetate injections require relatively frequent painful im injections. This led some researchers to investigate the longer-acting forms that were developed for prostate cancer and endometriosis. Early reports of the 11.25-mg every 3 months formulation indicated that it was highly effective, suppressing stimulated LH levels to under 3 U/L in 95% of subjects, with clinical suppression in all subjects (37). Subsequently, an investigation of 2 different monthly doses (3.75 and 7.5 mg) in conjunction with the 11.25-mg every 3 months dose demonstrated a statistically higher mean stimulated LH concentration in the 3-month group compared to both the 3.75- and 7.5-mg monthly groups (38). As in the previous study, no difference in measures of clinical progression was detected, and estradiol levels were similarly suppressed in all subjects.

Three recent studies have extended these observations (39–41). These studies had similar inclusion criteria and randomized assigned subjects to dosing groups. Outcome measures differed slightly but involved the frequency of suppression of stimulated LH levels at a specified time point as well as clinical assessments of growth, skeletal maturation, and breast development. The results of these studies are summarized in Table 3. In all studies, the 11.25-mg 3-monthly dose of leuprolide acetate was less effective at suppressing stimulated LH levels than the higher 3-monthly dose. Although in the small study by Mericq et al (41), 2 of the 4 subjects in the 11.25-mg group demonstrated modest clinical progression, this was not seen in the other much larger studies, which enrolled a total of 138 subjects. Growth rates were similar across all groups in all studies, and differences in bone age progression were not noted. Thus, although the 11.25-mg 3-monthly preparation did not provide as much hormonal suppression, this may not be an accurate indicator of the

Table 3. Percentage of Subjects Demonstrating Biochemical Suppression While Receiving Extended-Release Leuprolide Acetate

	Mericq *et al.* (41), n = 14		Fuld *et al.* (39), n = 54		Lee *et al.* (40), n = 84	
	n in group	Percent biochemical suppression (peak LH ≤ 4 U/L)	n in group	Percent biochemical suppression (peak LH ≤ 4 U/L)	n in group	Percent biochemical suppression (peak LH ≤ 4 U/L)
7.5 mg monthly	5	80	19	94		
11.25 mg 3-monthly	4	75	21	67	42	78
22.5 mg 3-monthly	5	100	14	92		
30 mg 3-monthly					42	95

overall efficacy. Longer studies will be required to determine any differences among the preparations in terms of clinical suppression of pubertal development, bone age advancement, and height outcomes.

Peripheral precocious puberty

In contrast to CPP, treatment of PPP depends on the cause. Recent data have been published on 2 rare but fascinating causes of PPP, FMPP, and MAS. FMPP is due to an activating mutation in the gene encoding the LH receptor. Affected boys have precocious pubertal development associated with minimal increases in testicular volume and an autosomal dominant, sex-limited inheritance pattern. Treatment has involved androgen receptor blockade and aromatase inhibition to limit clinical signs of androgen excess and excessive skeletal maturation (42). In the past, treatment has included ketoconazole, which is associated with decreased glucocorticoid production and hepatotoxicity. Androgen receptor blockade with spironolactone and aromatase inhibition with testolactone have been shown to be effective treatments, although both drugs require multiple daily dosing. The BATT study (Bicalutamide and Anastrozole Treatment of Testotoxicosis), a multicenter, 1-year, industry-sponsored study of 14 boys with FMPP using the newer androgen receptor antagonist bicalutamide along with the third-generation aromatase inhibitor anastrozole, found that these agents were effective in slowing growth velocity and bone age advancement with once daily dosing (43). Few long-term data are available, but 1 report of 2 boys treated with these agents for 4.5 and 5 years indicated continued suppression of androgenic findings, slower bone age progression, and increased predicted adult height (44). Progression to CPP is common, and addition of GnRHa is often required. The BATT study is planned to extend until adult height is attained.

Treatment of the precocious puberty associated with MAS is challenging. MAS is due to somatic activating mutations of the GNAS gene encoding the Gsα protein, part of the heterotrimeric G protein system. The classic triad of the condition is polyostotic fibrous dysplasia, café au lait macules of the skin, and precocious puberty, which is far more common in affected girls than in boys. The condition is extremely heterogeneous, with some girls having waxing and waning breast development with or without isolated episodes of vaginal bleeding and minimal bone age advancement and others having progressive pubertal maturation and frequent bleeding. Attempts at treatment have focused on aromatase inhibition or partial estrogen receptor blockade (45). Most of these agents have demonstrated inadequate efficacy or have been associated with increased ovarian or uterine size, calling into question their long-term safety. However, in a small study, the third-generation aromatase inhibitor letrozole appeared to decrease vaginal bleeding, growth velocity, and bone age advancement without change in ovarian volume (46). One subject in this trial experienced ovarian torsion associated with a large cyst. A recently published clinical trial of fulvestrant, a pure estrogen receptor blocker, showed promising results (47). This multicenter international study enrolled 30 girls with MAS at an average age of 5.9 years. Monthly im injections of fulvestrant were administered at a dose of 4 mg/kg. Subjects were treated for 1 year, and 29 completed the study, with 24 electing to enter an extension phase. Of those with vaginal bleeding at baseline, 74% experienced at least a 50% reduction in the number of days with bleeding, with the median number of bleeding days decreasing from 12 to 1 per year. The rate of skeletal maturation, defined as change in bone age over change in chronological age ($\Delta BA/\Delta CA$), decreased from 1.99 at baseline to 1.1 at 1 year. There was no difference in predicted adult height. There were no changes in uterine or ovarian volumes, and no changes in the frequency of ovarian cysts. Long-term safety and efficacy have yet to be determined for this treatment, and additional studies are clearly needed. Boys with precocious puberty due to MAS may benefit from treatment with the agents used in FMPP.

Outcomes of Treatment

Height

The effect of GnRHa treatment of CPP on height outcomes is typically greater in those experiencing the onset

of puberty before 6 years (30). Variation in height outcomes among studies may be in part additionally related to incomplete follow-up, lack of adequate control groups, method of height prediction, and variable definitions of adult height. A number of studies have been reported in the last 2 years that assessed adult height after treatment (48–51), but these largely confirm previous findings.

Reproduction and metabolic outcome

Many studies have reported long-term reproductive outcomes of girls treated for CPP with GnRHa (reviewed by Carel et al in Ref. 30). Measures assessed have included regularity of menstrual cycles, pregnancy rates, and live births. These findings were confirmed in 2 recently published studies. In an industry-sponsored clinical trial, Neely et al (52) recontacted 20 female subjects out of a cohort of 49 girls treated for CPP for an average of 3.5 years. The age at follow-up ranged from 18–26 years. Eighty percent had normal menstrual cycles. There were 12 pregnancies among 7 women, and there were 6 live births with 5 spontaneous or elective terminations and 1 ongoing pregnancy. These figures were not deemed different from the normal population. Magiakou et al (50) provided follow-up on 47 women seen for CPP, 33 of whom were treated with GnRHa and 14 of whom elected not to receive treatment. There was no difference between the groups in the incidence of menstrual irregularity, significant dysmenorrhea, number of pregnancies, or pregnancy outcome.

There have been concerns that PCOS occurs more often in those with CPP (30) than in those with normal puberty, although reported frequencies vary. In a carefully designed study published in 2010, the investigators recruited 46 young women from their clinic population who met strict criteria for idiopathic CPP (53). All had been treated with GnRHa. Subjects were evaluated at a mean age of 18.1 ± 3.0 years and had menarche at 12.2 ± 0.93 years. Subjects had a structured interview, physical examination, laboratory evaluation, and a pelvic ultrasound during the early follicular phase of their menstrual cycles and kept diaries of their menstrual patterns. Using the Rotterdam criteria, the prevalence of PCOS was 32%. A major drawback was the lack of a control group, but the reported prevalence is well above that expected for healthy young women (54). There were no predictive factors for the development of PCOS, including birth weight, body mass index (BMI) at diagnosis, and age at onset of pubarche or thelarche. In another study, 21% of subjects evaluated between ages 16 and 32 had PCOS by the National Institutes of Health criteria, but there was a relatively low recruitment rate, potentially biasing the results (50). At baseline, girls with CPP have higher BMI SD scores for age, and this pattern persists throughout treatment. Some studies have identified subsets of subjects with high homeostasis model of assessment for insulin resistance (HOMA-IR) scores after treatment, suggesting increases in cardiometabolic risk. This seems to be related to higher gains in BMI (53, 55), but there are very few data. Differing diagnostic criteria, race/ethnicity, age at follow-up, and potential for bias make comparison of studies difficult, but concern continues for long-term endocrine and metabolic outcomes.

Psychological

Many families are concerned about adverse psychosocial effects of precocious puberty. It is remarkable that only a few studies have evaluated psychological outcome in adolescents or adults who had precocious puberty, particularly because this is a common reason for families to seek treatment and for providers to give it. There is a wealth of data regarding long-term behavioral and emotional outcomes of girls with puberty occurring in the normal time frame but earlier than average, and these generally point to more frequent risk-taking and delinquent behaviors, earlier sexual debut, and more sex partners (56, 57). However, the relevance of these studies to those with truly precocious puberty is unclear. The only 2 studies examining the effect of GnRHa on psychological outcomes of girls with CPP showed no consistent abnormalities at baseline and variable treatment effects among subjects (58, 59), but these were both published more than 10 years ago. More long-term studies of this population are clearly needed.

Conclusions

Precocious puberty is a common problem seen in pediatric endocrinology practice. Identification of the child with pathological pubertal development allows for accurate diagnosis and application of current treatment strategies. Recent improvements in therapeutic agents allow for complete suppression of CPP with less discomfort to the patient and improvement of height outcomes, particularly in those less than 6 years old. Our major gaps in understanding lie in the area of long-term outcomes, including endocrine and metabolic effects of precocious puberty. The most striking deficit is the lack of long-term data on the psychological and behavioral effects of precocious puberty and the effects of GnRHa treatment. We can anticipate additional information on these aspects in the years to come.

Acknowledgments

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