

Precocious Puberty: Aspects of Diagnosis and Treatment

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Early pubertal development (see sidebar, *Key Points: Onset of Puberty*) is diagnosed when puberty begins younger than the lower limit of age of onset. Approximations for this age for girls in the United States from the NHANES (National Health and Nutrition Examination Survey) database are 8.0 years for white girls, 6.6 years for African American girls, and 6.8 years for Latina girls. Extrapolation of the available data for boys suggests the early limit of development approximating 9.0 years for white boys, 8.0 years for African American boys, and 9.5 years for Latino boys. Hence, it is not possible to determine an exact date when puberty is early. Practically, each presentation with the complaint of early puberty must be evaluated individually, with particular attention to rate of progression.

Data recently summarized¹ for girls suggest a continuation of the secular trend toward an earlier age but fail to verify this, whereas data for boys are inadequate to interpret. It has also been suggested—but not verified—that among girls, there is a relationship between the onset of puberty and obesity. This is based upon early breast development, however, which may be difficult to ascertain, particularly in the somewhat heavy girl with fullness of the chest area. Palpation of firm tissue beneath the areolae is indicative of breast development and soft tissue beneath the areolae compared with surrounding subcutaneous tissue does not. It has not been shown that such early breast budding is in fact the onset of puberty as substantiated by either the demonstration of secretion of pubertal levels of gonadotropins and estradiol or normal progression of puberty. Even if there is earlier onset of breast development, such progresses very slowly, and puberty is not being completed earlier than during recent decades, further suggesting that the initial minimal breast development is a consequence of minimal increases in estrogen stimulation, which may be related to a greater proportion of adipose tissue rather than the pubertal increase in activity of the

KEY POINTS: ONSET OF PUBERTY

- Minimal pubertal changes such as protruding areolae and a few sexual hairs do not necessarily indicate the onset of puberty.
- Determination of the onset of breast development cannot always be ascertained by visual inspection of the chest; palpation of a disk of tissue beneath the areolae firmer than the surrounding tissue strongly suggests breast development. On examination, palpation pressing from the areolae with less dense tissue than surrounding tissue (donut sign) fails to indicate breast tissue.
- Onset of puberty in girls usually presents with increase in nipple diameter and protrusion or tenting of the areolae.
- The first clinical evidence of puberty in boys is increase in testicular volume to greater than 4 cc. or more than 2.0 cm in long axis.
- Puberty involves progressive breast and pubic hair changes in girls together with an accelerated growth rate.

hypothalamic-pituitary-ovarian axis.

Precocious puberty is diagnosed when physical changes of puberty occur; the first evidence is usually breast development in girls and genital growth in boys. Hence, it is pertinent to verify in girls that chest fullness is in fact breast development, most clearly manifest by disks of firm tissue centered beneath the areolae and protrusion and increased diameter of nipples. Findings include not only the onset progression of physical changes of puberty but also acceleration of linear growth and skeletal maturity.

Precocious puberty can be classified as either central precocious puberty (CPP) or peripheral precocious puberty (PPP). CPP is physiologically normal puberty occurring early as a consequence of reactivation of the hypothalamic-pitu-

itary-gonadal (HPG) axis. Pituitary gonadotropin secretion results from increased frequency and amplitude of the episodic release of gonadotropin-releasing hormone (GnRH) secretion. Activated gonads, which secrete hormones, cause the physical changes of puberty, stimulate a premature pubertal growth spurt and sperm maturation in boys, and follicular maturity in girls. CPP is much more common among girls, usually with no underlying abnormality. CPP in boys, as normal puberty, presents with increased testicular volume of >4 cc. An underlying abnormality, most commonly of the central nervous system, is more frequently present among boys compared with girls with CPP. CPP as a consequence of radiation or chemotherapy occurs among male and female oncology patients. It may be accompanied by anterior pituitary or endocrine end-organ deficiencies, particularly growth hormone deficiency.

Initial assessment of precocious puberty involves a careful review of growth to ascertain acceleration of growth rate, verification of general findings on physical examination with a record of Tanner staging of puberty, measurement of serum levels of gonadotropins, particularly luteinizing hormone (LH) and estradiol in girls and testosterone in boys, and, if growth acceleration or progression of pubertal changes are present, a roentogram of the hand and wrist for bone age determination.

PERIPHERAL PRECOCIOUS PUBERTY

Diagnosis. PPP is a consequence of stimulation from hormones present independent of activation of the HPG axis (see sidebar, *Pertinent Findings in PPP*). PPP, which is less common than CPP, is usually a consequence of sex steroids from a pathophysiologic or autonomous source, most commonly congenital adrenal hyperplasia among boys. These rare sources of sex steroids are adrenal, gonadal, or from differentiated neoplastic tissues. Activating mutations are associated with PPP in McCune-Albright syndrome (MAS) (Figure 1) and in familial male-limited gonadotropin independent precocious puberty (FMPP) (activating mutations of the LH receptor). Gonadotropin (hCG)-producing tumors are associated with precocious puberty among males but not females.

Therapy. Treatment of PPP involves primary therapy for the underlying cause and use of agents to block production or action of sex steroids. Such therapy involves primary therapy if available for the underlying cause when present, but it is usually difficult and without complete effectiveness, involving the use of agents to block production or action of sex steroids. Examples of the former include surgical resection of tumors and glucocorticoid treatment of congenital adrenal hyperplasia and of the latter are noted later concerning MAS and FMPP. Because PPP is a consequence of sex steroid stimulation from sources other than early activa-

tion of the HPG axis, GnRH analogues (GnRHa) are ineffective in treatment. A consequence of continued exposure to elevated sex steroid levels of PPP is an eventual progression via activation of the HPG axis to CPP. When this occurs, GnRHa therapy should be considered as a treatment option.

Historically, treatments of precocious puberty in girls associated with MAS, such as progestational agents, were only moderately effective. Currently, third-generation aromatase inhibitors, compounds that attach to the cytochrome P450 portion of the aromatase enzyme and prevent conversion from androgens to estrogens reducing the serum levels of estrogens, are being studied.^{2,3} Tamoxifen, a selective estrogen-receptor modulator, diminishes estradiol production and stops pubertal progression,⁴ although it is associated with unexplained uterine volume increase.⁵ A pure estrogen receptor antagonist, fulvestrant (Faslodex, AstraZeneca), is being investigated for

PERTINENT FINDINGS IN PPP

- Results from sex steroid stimulation from a source other than activity of the HPG axis
- Source of sex steroid may be by autonomous production from the ovaries or testes, from the adrenal cortex, differentiated malignant tumors or exogenous. Endocrine disruptors, compounds that have properties to stimulate hormone production or occupy sex steroid hormone receptors have not been shown to have significant enough impact to cause PPP.
- Hence, typically gonadotropins (luteinizing hormone and follicle-stimulating hormone) are within or suppressed below the prepubertal range, and sex steroids, estradiol in females and testosterone in males usually are within the pubertal range.
- Causes include congenital virilizing adrenal hyperplasia and activating LH-receptor mutations (familial male-limited gonadotropin independent puberty [FMPP]) gonadotropin (hCG)-producing tumors in among males, McCune-Albright syndrome (MAS), gonadal and adrenal tumors, and prolonged exposure to exogenous steroids in both sexes.
- Prolonged stimulation of sex steroid associated with PPP may result in secondary CPP.
- Treatment, except for adrenal enzyme deficiencies and tumors that should be specifically treated, such as surgery when appropriate, primarily involves blocking the production of the sex steroid or the steroid receptor.

efficacy in halting vaginal bleeding and skeletal maturation in girls with MAS. Currently, however, there is no known completely effective treatment for PPP in girls with MAS.

MAS in boys is less common than in girls and is usually diagnosed at an older age. Treatment of PP in boys with MAS is similar to treatment of FMPP; the goal is to either inhibit the production or effect of adrenal and testicular androgens. Various therapeutic agents such as ketoconazole, spironolactone, and aromatase inhibitors (AIs) have been tried with marginal success.⁶⁻⁸ A pilot study of FMPP treatment with the nonsteroidal antiandrogen, bicalutamide and the third-generation AI, anastrozole (Arimidex, AstraZeneca), was associated with decreased growth velocity and skeletal maturation, but further studies are anticipated and needed.⁹

CENTRAL PRECOCIOUS PUBERTY

Diagnosis. Prior to deciding if treatment is warranted for CPP, it must be verified that the CPP is progressive rather than simply early onset of relatively minor physical changes, such as breast budding (nonprogressive) or normal puberty with early onset and normal growth potential.¹⁰

Progressive CPP (see sidebar, *Diagnosis and Treatment of CPP*) is diagnosed by documentation of progression of early pubertal development (Figure 2) and accelerated linear growth rate; pubertal gonadotropin secretion using either basal, GnRH, or GnRHa-stimulated levels; and an advanced skeletal age or accelerating rate of maturity. If random gonadotropin levels are not clearly pubertal, this must be verified using GnRH or GnRHa-stimulation testing.

Although not usually necessary, ovarian and uterine size visualized by pelvic ultrasound may be useful in the differentiation of CPP from nonprogressive forms of early puberty. Indications for GnRHa treatment of CPP relate to the untimely physical and psychosocial consequences of early puberty. All children with progressive CPP should be considered for GnRHa therapy. The most



Figure 1. Breast development in a 4-year-old female with McCune-Albright syndrome.



Figure 2. Evidence of progression of early onset of breast development in a 5-year-old girl.

frequent reasons for parents requesting therapy is to delay pubertal changes to allow the child to grow and develop similar to peers and to preclude or reclaim adult height potential. Before therapy, in addition to verifying that puberty is progressive and gonadotropin secretion is pubertal, height, growth rate, skeletal age, and predicted adult height in relation to target (genetically expected) height should be considered.

Treatment. The only effective therapy for CPP is a GnRHa. GnRHa occupies and downregulates the GnRH receptors on the pituitary LH and FSH-secreting cells within the pituitary, blocking GnRH leading to cessation of pubertal development. Therapy with GnRHa has been demonstrated to halt progression of physical pubertal changes (Figure 3) and stop or preclude menarche. If begun early, tall stature during childhood and foreshortened adult height is precluded. Among those with advanced bone age at onset of therapy, treatment is followed by slowing of bone age maturity with progressive reclamation of

diminished growth potential.¹¹ Both the patient and parents should be informed of the goals of therapy to stop or cause regression of pubertal development, including menstruation in girls, to attempt to gain genetically expected height potential, and to avoid psychosocial stresses related to earlier maturity than their peers. The decision regarding GnRHa treatment should be made with the parents considering their child's psychosocial as well as physical maturity. Most frequently, for parents of children that have markedly early or rapidly progressive puberty, parents chose GnRHa therapy. GnRHa therapy, by obstructing the GnRH-stimulated gonadotropin release, is the only highly effective treatment. GnRHa therapy is available as a depot injection used at 1 or 3 monthly intervals, as a subcutaneous implant,¹² a daily subcutaneous injections, and a nasal spray.

If the family concludes that early puberty is not a problem and need not be interrupted, therapy is not appropriate. This is a reasonable conclusion if there is not evidence of fore-

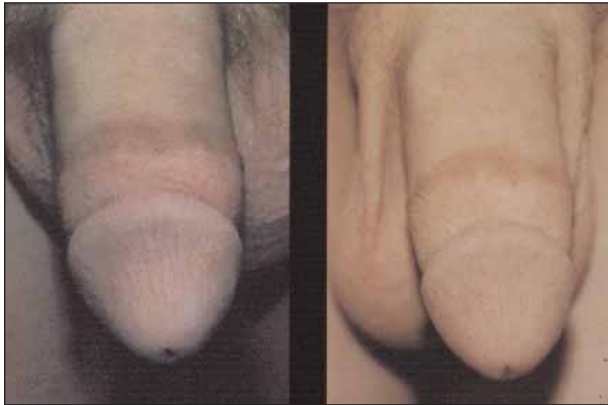


Figure 3. Genital development and pubic hair in a boy with central precocious puberty before (left) and after GnRH therapy. Note regression of pubic hair, testicular volume also diminished.

shortening of expected adult stature. In fact, there is evidence that if adult height in a girl is predicted to be >155 cm, there may be limited benefit from therapy.¹¹ Such can be considered to be slowly progressing precocious puberty, a situation in which GnRH therapy is usually considered not to be indicated.

PREMATURE THELARCHE

Premature breast development without other pubertal changes is called *premature thelarche*. Most commonly, this occurs during infancy and should be considered a variant of normal related to increased ovarian activity in the neonatal period. Breast development may represent a persistence of palpable breast tissue present at birth. This often regresses by 12 months of age but may persist to 24 months or beyond. Thelarche present older than 24 months is associated with increased FSH and inhibin B secretion indicative of enhanced follicular development¹³ and is related to somewhat greater estradiol secretion than is typical of childhood.¹⁴

When a girl presents with breast development but no other evidence of puberty, careful monitoring is indicated, as this might be the first evidence of CPP.¹⁵ When breast development is minimal without dramatic progression and growth rate is documented to be normal for a prepubertal child during recent months, assessment usually involves observation without laboratory testing. It is, however, useful to consider early pubertal changes to extend along a continuum from premature thelarche, non-PPP to CPP. Although it is the exception to have progression along this continuum, when development at presentation suggests the diagnosis of premature thelarche, it is appropriate to consider obtaining studies so that progression can be recognized in a timely fashion. Hence, serum LH, FSH, and estradiol levels

DIAGNOSIS AND TREATMENT OF CPP

- CPP involves both the early onset (usually breast development in girls and increased testicular volume in boys) followed by progression of changes.
- Maturity of pubertal sexual characteristics is accompanied by an accelerated linear growth rate and skeletal maturation.
- Natural history results in physical maturity including potential for fertility and tall stature in childhood but foreshortened adult height.
- Initial testing involves gonadotropins, primarily LH, and testosterone in boys and estradiol in girls. LH in the pubertal range using a third-generation assay with sex steroid within the range of early puberty or above is consistent with CPP.
- Reasons to treat are to allow the child to grow and develop as appropriate for peers of their age and gender and to preclude excessive growth in height during childhood and diminished adult height.
- The only completely effective therapy is timely suppression of puberty using GnRH.

and a skeletal age radiograph may be obtained.

PREMATURE ADRENARCHE

Pubertal-related increase in adrenal androgen production (adrenarche) can be documented by identifying pubertal levels of the weak adrenal androgen dehydroepiandrosterone sulfate (DHEA-S). This rise is commonly detectable as young as 6 years of age. Early development of sexual hair, referred to as *premature pubarche*, most commonly is a consequence of premature adrenarche. Premature adrenarche occurs independently of the onset of puberty.¹⁶ Other androgen-induced changes can include early onset of adult-type body odor, oily skin and acne, and axillary hair, which in fact may precede pubic hair development. Height and skeletal age may be advanced with premature adrenarche so growth before the onset of puberty may be accelerated, but growth during puberty is less so that adult height is not altered. Premature pubarche is more common among girls than boys, and it is important to realize that premature pubarche may be the first evidence of adrenal or ovarian androgen excess,¹⁷ including polycystic ovarian disease.¹⁸ The association of increased body mass index and early onset of sexual hair may later manifest in hyperinsulinism and the metabolic syndrome.

Whereas a single DHEA-S level within the early pubertal

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range is indicative of premature adrenarche, there may be instances in which androgen changes are untimely enough so that more laboratory evaluation is needed. Such may include DHEA, androstenedione and testosterone concentrations, and if findings suggest hyperinsulinism, concomitant glucose and insulin levels. Excessive virilization in both sexes, including clitoromegaly and hirsutism in girls, mandates further evaluation for hyperandrogenic states, including congenital adrenal hyperplasia, with consideration of measurement of 17-hydroxyprogesterone, androstenedione, testosterone, free testosterone, cortisol, and LH and FSH levels. Markedly severe virilization may be associated with rare adrenal- or ovarian androgen-secreting tumors. If virilization, skeletal age and growth rate are excessive, an underlying abnormality should be ruled out. ■

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1. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics*. 2008;121:Suppl 3:S172–191.
2. Mieszczak J, Lowe ES, Plourde P, Eugster EA. The aromatase inhibitor anastrozole is ineffective in the treatment of precocious puberty in girls with McCune-Albright Syndrome. *J Clin Endocrinol Metab*. 2008; Apr 8. [Epub ahead of print].
3. Feuillan P, Calis K, Hill S, et al. Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome: a pilot study. *J Clin Endocrinol Metab*. 2007;92:2100–2106.
4. Eugster EA, Shankar R, Feeze LK, Pescovitz OH. Tamoxifen treatment of progressive precocious puberty in a patient with McCune-Albright syndrome. *J Pediatr Endocrinol Metab*. 1999;12:681–686.
5. Eugster EA, Rubin SD, Reiter EO, et al. Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multicenter trial. *J Pediatr*. 2003;143:60–66.
6. Laue L, Kenigsberg D, Pescovitz OH, et al. Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med*. 1989; 320:496–502.
7. Laue L, Jones J, Barnes KM, Cutler GB, Jr. Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab*. 1993;76:151–155.
8. Almeida MQ, Brito VN, Lins TS, et al. Long-term treatment of familial male-limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. *Clin Endocrinol (Oxf)*. 2007; Dec 17. [Epub ahead of print].
9. Kreher NC, Pescovitz OH, Delameter P, et al. Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole. *J Pediatr*. 2006;149:416–420.
10. Antoniazzi F, Zamboni G. Central precocious puberty: current treatment options. *Paediatr Drugs*. 2004;6:211–231.
11. Adan L, Chemaitilly W, Trivin C, Brauner R. Factors predicting adult height in girls with idiopathic central precocious puberty: implications for treatment. *Clin Endocrinol (Oxf)*. 2002;56:297–302.
12. Eugster EA, Clarke W, Kletter GB, et al. Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. *J Clin Endocrinol Metab*. 2007;92:1697–1704.
13. Crofton PM, Evans NE, Wardhaugh B, et al. Evidence for increased ovarian follicular activity in girls with premature thelarche. *Clin Endocrinol (Oxf)*. 2005;62:200–209.
14. 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;134:190–192.
15. Pasquino AM, Pucarelli I, Passeri F, et al. Progression of premature thelarche to central precocious puberty. *J Pediatr*. 1995;126:11–14.
16. Ghizzoni L, Milani S. The natural history of premature adrenarche. *J Pediatr Endocrinol Metab*. 2000;13(Suppl)5:1247–1251.
17. Siegel SF, Finegold DN, Urban MD, et al. Premature pubarche: etiological heterogeneity. *J Clin Endocrinol Metab*. 1992;74:239–247.
18. Ibanez L, Potau N, Dunger D, de Zegher F. Precocious pubarche in girls and the development of androgen excess. *J Pediatr Endocrinol Metab*. 2000;13(Suppl)5:1261–1263.