



Evaluation and Referral of Children With Signs of Early Puberty

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Concerns about possible early pubertal development are a common cause for referral to pediatric medical subspecialists. Several recent studies have suggested that onset of breast and/or pubic hair development may be occurring earlier than in the past. Although there is a chance of finding pathology in girls with signs of puberty before 8 years of age and in boys before 9 years of age, the vast majority of these children with signs of apparent puberty have variations of normal growth and physical development and do not require laboratory testing, bone age radiographs, or intervention. The most common of these signs of early puberty are premature adrenarche (early onset of pubic hair and/or body odor), premature thelarche (nonprogressive breast development, usually occurring before 2 years of age), and lipomastia, in which girls have apparent breast development which, on careful palpation, is determined to be adipose tissue. Indicators that the signs of sexual maturation may represent true, central precocious puberty include progressive breast development over a 4- to 6-month period of observation or progressive penis and testicular enlargement, especially if accompanied by rapid linear growth. Children exhibiting these true indicators of early puberty need prompt evaluation by the appropriate pediatric medical subspecialist. Therapy with a gonadotropin-releasing hormone agonist may be indicated, as discussed in this report.

INTRODUCTION

Concerns about early pubertal development are a common cause of parental anxiety in pediatric primary care offices and are a major reason for referrals to pediatric endocrinologists. Although a small number of such children have a disorder that requires thorough testing and treatment, the great majority of patients have benign, normal variants of puberty, some of which can be followed by the primary care provider without immediate testing or referral. In addition, confusion still exists regarding what can be considered normal timing of puberty, as more studies confirm that the mean age at onset of breast and pubic hair

abstract

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development is occurring younger than the age that was previously considered normal.¹⁻³ The purpose of this report is to update primary care physicians (PCPs) on what is known about the timing of puberty and to review the features of the benign normal variants of puberty and how they differ from the child with central precocious puberty (CPP) who might be considered for treatment.

Puberty is triggered when the hypothalamus begins to increase its pulsatile secretion of the peptide gonadotropin-releasing hormone (GnRH), which stimulates the production of the 2 gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH stimulates the ovaries to secrete estradiol and the testes to secrete testosterone, and FSH promotes the development of the oocytes or spermatozoa and increases the size of the gonads. This activation of the hypothalamic-pituitary-gonadal (HPG) axis is referred to as gonadarche. Estradiol causes progressive breast enlargement, the pubertal growth spurt, and rapid bone age advancement, and testosterone causes penile enlargement and pubic hair growth in boys and, by conversion to estradiol, causes the male growth spurt. It is important to note that pubic hair in girls and adult axillary odor in boys and girls is related to the increase in secretion of weak adrenal androgens (primarily dehydroepiandrosterone-sulfate [DHEA-S]), referred to as adrenarche, and is unrelated to activation of the HPG axis. Thus, as discussed later in the report, it is not unusual for a child to have pubic hair and/or axillary odor a few years before the onset of true, central puberty.

HOW DO CHANGES IN THE TIMING OF PUBERTY AFFECT MANAGEMENT OF EARLY PUBERTAL DEVELOPMENT?

When presented with a child who might be maturing too early, it helps

to understand the normal timing of gonadarche and the changes that have occurred over the past 50 years. Although there has been a well-documented decrease in the age of onset of menarche and probably puberty as well, over the past 2 centuries, studies have indicated that this trend stabilized in the 1950s, with little change over the next 20 to 30 years. In the standard pediatric textbooks, puberty is considered precocious if it starts before 8 years of age for girls and before 9 years of age for boys. These cutoffs were challenged after an American Academy of Pediatrics study was published, titled "Secondary Sexual Characteristics and Menses in Young Girls Seen in Office Practice: A Study From the Pediatric Research in Office Settings Network (PROS)".¹ It was reported that the mean age of appearance of breast development (~11 years in studies before 1980) was close to 10 years in white girls and about 9 years in black girls. Furthermore, approximately 15% of black girls and 5% of white girls between 7 and 8 years of age already had breast development. Because of methodologic issues in the study design and the concern that accepting a lower cutoff would result in missed cases of endocrine abnormalities,⁴ the traditional cutoffs are still accepted by many pediatric endocrinologists. However, similar findings were reported in the NHANES from 1988 to 1994 using a population of 8- to 16-year-old girls designed to be representative of the entire US population.² In a more recent study,³ using a sample of white, black, and Hispanic girls in New York City, Cincinnati, and San Francisco, breast development was assessed by palpation, allaying the concern (one of the problems with the PROS study) that lipomastia might have been confused with early breast development. They reported that in a sample of 7- to 8-year-old girls, 23% of black, 15% of Hispanic, and 10% of white girls

had breast development. All 3 of the aforementioned studies, as well as others, have highlighted the ethnic/racial differences in the timing of pubertal onset as well as the observation that overweight children appear to undergo earlier breast and pubic hair development and somewhat earlier menarche than do girls of normal weight.⁵ Thus, the evaluation of girls with signs of early puberty has to take into account increased BMI as well as race/ethnicity. Because most PCPs feel comfortable with the traditional cutoff of 8 years, it seems reasonable for PCPs to consider referring most girls who have breast development (confirmed by palpation) before 8 years of age. However, the majority will not have true endocrine pathology but represent the lower end of the new normal range for sexual maturation. It is also apparent that some girls with early puberty have a slowly progressive or nonprogressive form, so the rate at which puberty advances is another important variable that can affect the level of concern. Several studies have shown that boys with CPP, using a cutoff age of <9 years, have a higher incidence of central nervous system (CNS) findings than do girls (8 of 24, or 33% in 1 recent study⁶). Thus, penile and/or testicular enlargement in boys before 9 years of age is concerning. A recent study by the PROS network looking at over 4000 boys in 144 practices found data suggestive of earlier onset of puberty in contemporary US boys using a definition for puberty of testicular volume ≥ 3 cc⁷; however, due to a lack of a past gold standard for pubertal onset in US boys, this requires further studies before definitive conclusions can be reached.

GENERALLY BENIGN VARIANTS OF EARLY PUBERTAL DEVELOPMENT

Premature Adrenarche

Adrenarche, an adrenal maturational event associated with an increase in secretion of DHEA and its more abundant storage form, DHEA-S, is associated with the appearance of pubic hair, axillary hair, and odor and sometimes mild acne. When these events occur before 8 years of age in girls or before 9 years of age in boys and are associated with a normal rate of growth (ie, tracking along the same percentile on the linear growth curve) and no evidence of clitoromegaly, penile growth, or testicular enlargement, the diagnosis is generally premature adrenarche (PA). As would be predicted from the earlier onset of pubic hair in black versus white girls in studies cited previously,¹⁻³ this diagnosis is particularly common in black girls.

Levels of DHEA-S are typically increased for age, usually in the range of 30 to 150 µg/dL. There is no activation of the HPG axis, and thus, FSH, LH, and estradiol or testosterone concentrations are at prepubertal levels. In 3% to 5% of cases of apparently benign PA, a mild, nonclassic form of congenital adrenal hyperplasia can present with similar features, but there is no consensus that such mild cases benefit from treatment. Nonclassic congenital adrenal hyperplasia is most often seen in patients of Ashkenazi Jewish and Hispanic background and is uncommon in black children. Rarely, virilizing adrenal or gonadal tumors can present with early pubic hair, but what distinguishes these pathologic states from typical cases of PA is the presence of clitoral enlargement or progressive growth of the penis and marked linear growth acceleration.

The extent of radiologic/laboratory testing needed for typical cases of PA is somewhat controversial. Many PCPs and pediatric medical subspecialists elect to have a

radiograph of the left hand and wrist performed to determine bone age. However, interpreting the results may require caution because the readings performed by radiologists who are less experienced with bone age review can differ from those performed by endocrinologists. Additionally, the diagnostic value of bone age radiographs was recently questioned in a retrospective study that found that bone age was advanced by 2 or more years in up to 30% of children with PA and that it had a low predictive value for pathologic states.⁸ Many subspecialists prefer to limit hormonal testing (including 17-hydroxyprogesterone to rule out the nonclassic form of congenital adrenal hyperplasia) to children who present with rapid growth and/or the red flags noted previously. Atypical or worrisome cases of early onset of pubic hair may suggest the need for referral to a pediatric medical subspecialist for further evaluation and testing.

Premature Thelarche

The typical presentation of premature thelarche (PT) is the appearance of palpable glandular tissue in girls aged younger than 2 years, which increases little or not at all over a period of many months and is not accompanied by crossing of growth percentile. In some girls, the amount of breast tissue may wax and wane. The etiology of PT is not clear. One theory is that PT is caused by small ovarian cysts that produce small amounts of estrogen transiently; as these cysts resolve over time, thelarche tends to stabilize or disappear. There is some controversy as to how often PT with onset before 2 years of age progresses to CPP, the extent of testing that is needed, and how closely such girls should be followed. One recent study of 450 Italian girls referred for PT at younger than 3 years identified CPP in only 2% and

peripheral precocious puberty in <1% but found no 1 test that could reliably identify only the girls with CPP.⁹ Because CPP in girls younger than 2 years is rare, it seems reasonable to hold off on hormonal testing and pelvic ultrasonography in most girls. Such children can be followed by PCPs without hormonal testing, but prompt referral to a pediatric medical subspecialist is indicated if the breasts increase in size over a 4- to 6-month period (especially if accompanied by growth acceleration) or if reassurance is needed.

Genital Hair Appearing in Infancy

This was once considered an unusual finding (reports in 1989 and 1992 described a total of 9 cases), but the appearance of genital hair in infancy seems to have increased in frequency in the past 2 decades. In the 4-year chart review study performed at a large urban hospital, 69 of 275 children younger than 3 years referred for signs of puberty (56 girls and 13 boys) had genital hair with no other signs of puberty.¹⁰ The hair is typically fine and straight and located more along the labia or over the scrotum, in contrast to older children with PA, in whom the hair is thicker, curlier, and located more over the pubic symphysis. Concentrations of testosterone and 17-hydroxyprogesterone were normal for age, but approximately half had a modest elevation of DHEA-S, suggesting an adrenal source of androgens. Although this situation often concerns parents, it is generally benign. If there is no genital enlargement and no crossing of growth percentiles, laboratory tests do not need to be ordered.

The finding of both genital hair and breast development in young children has become not infrequent, noted in 36 of 275 cases in the study mentioned previously. Although this combination might suggest a more serious underlying

disorder, hormone testing is usually reassuring, and follow-up of these children has not revealed rapid progression of findings or the need for treatment. Thus, referral is suggested, but again, prereferral hormone testing is not needed.

Lipomastia

An increasing number of girls who are overweight or obese are referred for concerns regarding early puberty on the basis of what appears to be breast tissue when the child is examined in the sitting position. However, when examined supine, the breasts are much less prominent, and careful palpation under the areolae fails to disclose firm glandular tissue. In addition, the nipples and areola will show no estrogenic stimulation. At times, even endocrinologists may have trouble determining whether there is a small amount of breast tissue or not. If the breast examination is inconclusive, the patient is unlikely to have progressive precocious puberty. Observation over a period of 4 to 6 months is, in most cases, reassuring.

Prepubertal Vaginal Bleeding

A less common and puzzling scenario is the young girl with 1 or 2 brief episodes of vaginal bleeding but no or little breast development, often referred to as premature menarche. Although trauma to the area, foreign body, infection, sexual abuse, or a vaginal or uterine tumor need to be considered, the history and the physical examination are generally completely benign. Recurrent or continuous bleeding are of greater concern. A recent series of 24 girls seen over a 5-year period found no evidence of endocrinopathy on the basis of pelvic ultrasonography or concentrations of LH, FSH, and estradiol.¹¹ All studies concerning prepubertal vaginal bleeding have reported spontaneous resolution after 1 to 6 episodes. It is suggested that these girls be referred to

a pediatric endocrinologist, gynecologist, or urologist if bleeding is heavy, recurrent, or continuous.

EVALUATION AND MANAGEMENT OF CENTRAL PRECOCIOUS PUBERTY

CPP is defined as the full activation of the HPG axis before 8 years of age in girls and before 9 years of age in boys. The diagnosis may be considered in girls who have progressive breast development and who cross percentiles upward on the linear growth chart. CPP is far less common in boys but may be considered if there is evidence of both testicular and penile enlargement before 9 years of age. The typical evaluation includes obtaining a family history, because CPP is occasionally inherited from the parents; menarche in the mother at 10 years or younger or a growth spurt in the father before 12 years of age are suggestive of autosomal-dominant inheritance. The family may be questioned about possible exogenous sources of sex steroids, including ingestion of oral contraceptive pills or exposure to transdermal estrogen creams or testosterone gels. There has been concern that exposure to environmental chemicals with estrogen-like activity, including phthalates or polychlorinated biphenyls, may cause early pubertal signs in girls, but firm evidence is lacking. Certain aromatic oils, such as lavender and tea tree oil, may also have estrogenic activity. The family should also be asked about any CNS symptoms, including severe frequent headaches or recent visual deficits, and a history of disorders associated with CPP, including brain tumor, meningitis, CNS trauma, cranial irradiation, hypoxic-ischemic injury, histiocytosis, and neurofibromatosis.

The physical examination in girls will focus on the Tanner stage of breast development and determination of whether there are supporting signs of

estrogen effect, including maturation of the nipples and areolae and a mucous vaginal discharge. Most girls seen for early puberty will be at the breast bud (Tanner 2) stage, but any girl with Tanner 3 development by 8 years of age is clearly progressing rapidly. In boys, voice change, acne, or facial hair may be other signs of significant androgen effect. Pubic hair, apocrine odor, and axillary hair in both boys and girls are typically related to adrenal androgen production, as noted previously, and are not reliable signs of CPP. If there is suspicion of a CNS tumor, visual field confrontation testing, optic funduscopy, and a detailed neurologic examination may be helpful.

The diagnostic evaluation of suspected CPP will typically include a bone age determination, which is often useful in predicting adult height. Most pediatric endocrinologists will insist on reading the radiographs themselves. Baseline laboratory testing may include FSH, LH, and either estradiol or testosterone. Severe hypothyroidism is a rare cause of CPP but is important to exclude if the growth velocity is slow instead of rapid. An LH of >0.3 IU/L is the most reliable screening test for CPP on a random blood sample, but if it is <0.3 and CPP is suspected, a stimulation test with a GnRH analog may be necessary. In selected cases, pelvic ultrasonography may be helpful because increased ovarian and uterine volumes relative to age are diagnostic of CPP, and it is particularly helpful if LH is suppressed and estradiol is high because it may reveal an ovarian tumor or a large ovarian cyst. Once the diagnosis of CPP is established, a computed tomography or MRI scan may be performed to determine whether there is a structural abnormality such as a hypothalamic hamartoma or a tumor in or near the pituitary. However, because the

positive yield of such studies is low (in 1 study a CNS abnormality related to CPP was found in only 2% of girls older than 6 years¹²), some reserve such imaging studies for girls whose puberty started before 6 years of age or if there are any CNS signs or symptoms. Because there is a higher incidence of CNS lesions in boys with CPP as noted previously, brain imaging is performed routinely in boys.

The use of GnRH analogs to treat CPP was recently discussed in a consensus statement developed jointly by the North American and European pediatric endocrine societies.¹³ One of the justifiable reasons for intervention is the preservation of height potential because untreated CPP may result in premature cessation of growth and resultant short stature. Short stature is more likely to occur if height is below the 50th percentile than if the height is \geq 90th percentile at the time of diagnosis of CPP. Treatment may be indicated if the predicted height, based on bone age, is less than 5 feet in a girl or less than 5 feet 5 inches in a boy, but studies suggest that benefit in terms of improved adult height is greater for those with puberty onset before 7 years of age. Other reasons to consider treatment for which there are no published studies include prevention of early menarche and the psychological ramifications that accompany it and suppression of sexual maturation in a girl who is emotionally immature. In cases in which puberty is progressive, menarche will usually occur at least 2 years after onset of breast development. Girls who are 10 years or older handle this much better than those who are 8 or 9 years old. In boys, treatment typically suppresses the hormonal changes that may result in aggressive or sexual behaviors.

Treatment with GnRH analogs such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion

of a subcutaneous histrelin implant. Leuprolide depot injections are often administered in the office of the PCP as a convenience to the family. Treatment is expensive (at least \$15 000 per year), so the decision to treat should not be taken lightly. In some instances, if the goals do not include preservation of linear growth potential but simply involve suppression of menses, as for some girls with significant developmental disabilities, there is a role for the substantially less costly drug, medroxyprogesterone depot, administered intramuscularly every 3 months. Whichever drug is chosen, it is important for the child to be seen by a pediatric endocrinologist at regular intervals. Clinical indicators that the medication is working include slowing of the growth velocity to <7 cm/year and shrinkage or softening of the glandular breast tissue or the testes. Many endocrinologists will also document suppression of the HPG axis via a GnRH stimulation test. The decision as to when to stop therapy is complex but typically occurs when it is apparent that continued pubertal suppression is no longer beneficial to the child. Thus, if the child is able to cope with puberty, and the predicted adult height is within the normal range, treatment may be stopped early; it often takes a year or more after cessation for menses to start. Some endocrinologists will end therapy in girls by 10 years of age, and others will continue it until 11 or 12 years of age, depending on clinical circumstances.

CONCLUSIONS

Although onset of signs of puberty before 8 years of age in girls and before 9 years of age in boys may be a sign of a serious underlying disorder requiring therapy, the majority of cases, especially in girls, are benign, normal variants that do not require extensive testing or treatment. It

is the task of the PCP to recognize cases in which the likelihood of significant pathology is greatest. In such cases, an informal consultation with a pediatric endocrinologist may assist the pediatrician in determining the necessity of referral and whether prereferral testing would be helpful. Girls at highest risk of pathology include those with onset of progressive breast development before 8 years of age, especially if accompanied by crossing of at least 1 linear growth percentile channel. Any boy with penile and/or testicular enlargement before 9 years of age is likewise at increased risk. When the only signs of sexual development are pubic and/or axillary hair and/or axillary odor, the source of androgens is almost always adrenal, which is usually benign if accompanied by normal linear growth.

Children with apparently benign variants of puberty provide a good opportunity for comanagement by pediatric medical subspecialists and PCPs. Options include observation at 4- to 6-month intervals to assess whether there is crossing of percentiles upward on the growth curve or clear progression of sexual maturation or referral to a pediatric medical subspecialist with expertise in disorders of early puberty for an initial evaluation with PCP follow-up. A pediatric endocrinologist or other appropriate subspecialist can target any investigations, including bone age interpretation and laboratory testing, to those who are most likely to have a more serious hormonal disorder.

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ABBREVIATIONS

CNS: central nervous system
CPP: central precocious puberty
DHEA-S: dehydroepiandrosterone-sulfate
FSH: follicle-stimulating hormone
GnRH: gonadotropin-releasing hormone
HPG: hypothalamic-pituitary-gonadal
LH: luteinizing hormone
PA: premature adrenarche
PCP: primary care physician
PROS: Pediatric Research in Office Settings Network
PT: premature thelarche

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