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Editorial: Precocious Puberty: Who Has It? Who Should Be Treated?

In this issue of *JCEM,* Palmert *et al.* (see page 415) (1), address the issue of whether all children with precocious puberty need treatment by reporting long-term follow-up data on 20 girls with unsustained or slowly progressive early puberty. This group of girls on the average achieved their genetic height potential and normal adult heights without treatment. Ten of the 20 girls had onset of puberty after 5 yr of age. Thirteen of the 20 girls had a bone age (BA) advance greater than 2 yr above chronological age (CA). None of the girls had GnRH-stimulated peak LH levels over 25 IU/L, and all had a GnRH-stimulated FSH peak greater than the LH peak. Unsustained precocious puberty was defined as no further pubertal development or regression of development as determined by a questionnaire. Slowly progressive puberty was also defined by questionnaire. This study once again demonstrates that not all girls with precocious puberty need treatment, and it raises these questions: What is precocious puberty? Who has precocious puberty? Which children should be treated?

What is precocious puberty and how is it treated?

Precocious puberty has most commonly been defined as the onset of puberty before the age of 8 yr in girls and before the age of 9 yr in boys. It involves not only early physical changes of puberty, but also linear growth acceleration and acceleration of bone maturation, which leads to early epiphyseal fusion and short adult height. Precocious puberty can be true or GnRH-dependent puberty, or it can be peripheral or GnRH-independent puberty. The questions raised by Palmert *et al* relate only to children with possible idiopathic true precocious puberty. Most girls (95%) with precocious puberty have idiopathic true precocious puberty. Boys more commonly (>50%) have an identifiable etiology for precocious puberty. The causes of true precocious puberty include central nervous system lesions, secondary to GnRH-independent precocious puberty, and idiopathic precocious puberty. The causes of GnRH-independent puberty include gonadal, adrenal, ectopic, or exogenous sources of hormone production. Adrenal causes include congenital adrenal hyperplasia (CAH) and tumors. Gonadal causes include McCune-Albright syndrome, familiar male precocious puberty, and tumors. Ectopic causes include human chorionic gonadotropin secreting tumors. Hypothyroidism may also cause GnRH-independent precocious puberty.

True precocious puberty involves activation of the hypothalamic-pituitary-gonadal axis (HPGA). Standard treatment of precocious puberty involves suppression of this axis with GnRH agonists (2). When precocious puberty is not idiopathic, treatment is based first on treating the underlying problem, and then may also involve treatment with GnRH agonists. For example, children with non-salt wasting CAH may present with precocious puberty. Appropriate management of CAH is initiated first, followed by further evaluation of the need for GnRH agonist therapy. A more detailed discussion of nonidiopathic precocious puberty is beyond the scope of this editorial. The remainder of this discussion relates to idiopathic precocious puberty.

Why should we treat precocious puberty?

Knowing why we treat idiopathic precocious puberty is integral to understanding the questions of whom should we treat. The only long-term complication of true idiopathic precocious puberty is compromised adult height. Adult height is improved with treatment (2, 3). Therefore, part of the decision of who to treat involves estimating adult height based on the child's current height and bone age, and comparing this predicted height with mid-parental height (MPH) and with the normal population. The other reasons to treat are psychosocial or behavioral. For example, a 4-yr-old with menses, even if she has a good predicted height, may deserve treatment. Or the 7-yr-old who is behind in school may deserve treatment so that she is not so far ahead of her peers and experiencing emotions related to hormonal changes that she cannot understand.

Is pubertal onset before age 8 yr in girls and 9 yr in boys an appropriate definition for precocious puberty?

The age definition of normal pubertal development is based on 95% of the population or 2 standard deviations (SD) below the mean age of pubertal onset in normal girls. Hence 2.5% of normal girls have onset of puberty before age 8. When puberty in girls begins between 6 and 8 yr, is it truly precocious puberty or simply at the outer limits of normal? Are there some girls for whom earlier onset is normal and others for whom it is precocious? Herman-Giddens *et al.* (4) have recently studied 17,077 girls and reported normal onset of puberty to be earlier than previously thought. In their population the mean age of breast development in African-American girls was 8.87 ± 1.93 yr (mean ± SD) and in white girls was 9.96 ± 1.82 yr. If the definition of precocious is 2 SD below the mean, then, based on this data, precocious puberty would be defined as onset less than 5 yr in African-American girls and onset less than 6.3 yr in white girls. However, this study did not have endocrine evaluations or follow-up data to determine if any of the girls with earlier development actually had precocious puberty.

What defines the onset of puberty?

Even after we define the time-frame for onset of precocious puberty, we still must ask, what defines onset of puberty?

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The physical changes of puberty are under the control of the HPGA. The HPGA activity increases with the onset of puberty as evidenced by increasing number and amplitude of spontaneous pulses of gonadotropins, luteinizing hormone (LH), and follicle stimulating hormone (FSH), plus increased peak LH and FSH levels in response to GnRH stimulation (5). Unfortunately, there is overlap in spontaneous and stimulated gonadotropin levels between prepubertal children and pubertal children, making interpretation of gonadotropin testing sometimes difficult. Interpretation of LH and FSH levels also depends on which gonadotropin assay is used. The newer ICMA assays have much lower levels and much greater sensitivity than the older RIAs. Because treatment of true precocious puberty is suppression of the HPGA with GnRH agonists, the axis must first have pubertal activity to warrant treatment. Thus, it is important to define what constitutes an active HPGA in order to say that true puberty has begun.

Simple premature thelarche involves only breast development, without pubic hair growth, without accelerated bone maturation, and with a normal height outcome, requiring no treatment. Simple premature adrenarche involves only pubic hair development, without the other manifestations of puberty, also requiring no treatment. It has been suggested that there is a continuum of puberty from premature thelarche through true precocious puberty (6). Pescovitz *et al.* (6) divided girls into 6 groups: 1) isolated breast development, no pubic hair, no growth spurt, and no bone age (BA) advancement; 2) breast development and BA advance, but no pubic hair or growth spurt; 3) breast development and pubic hair, but no BA advance or growth spurt; 4) breast development, growth spurt, and BA advance, but no pubic hair; 5) breast development and pubic hair and either growth spurt or BA advance; and 6) breast development and pubic hair and both growth spurt and BA advance. Groups 1 and 2 had FSH predominant responses to GnRH testing. Group 6 had LH predominant responses to GnRH testing. However, there was variability in the LH and FSH responses to GnRH testing in the intermediate groups. Some girls had LH predominant responses, and some had FSH predominant responses. Palmert *et al.* (1) describe girls with slowly progressing or unsustained puberty. Some of their patients fall in the intermediate groups described by Pescovitz *et al.* (6) which further illustrates the spectrum of pubertal changes physically and biochemically as well as the need for clinicians to distinguish between patients when making decisions about treatment.

Palmert *et al.* report girls with both early breast development and early pubic hair growth. Most of the girls were tall for CA but short for BA, which usually predicts a shorter adult height outcome. However, all girls had a prepubertal response to GnRH stimulation and were, therefore, not considered candidates for treatment with GnRH analogues. A prepubertal response to GnRH stimulation was defined by Palmert's *et al.* criterion of FSH peak greater than LH peak and LH peak less than 25 IU/L (measured by RIA using the 2nd IRP-hMG LH standard). Most of the girls in their study also had no detectable peaks of spontaneous nocturnal LH secretion. Palmert *et al.* appropriately note this is an older less sensitive LH assay and that newer gonadotropin assays may help further define the gonadotropin secretion in similar girls. It is also important to note that others might use different criteria to interpret the GnRH tests. This illustrates another problem in defining the onset of puberty. There is no single level of LH, FSH, or estradiol with 100% specificity and 100% sensitivity for precocious puberty. We previously reported a peak LH level of more than 15 IU/L or a peak LH-to-peak FSH ratio of more than 0.66 as criteria for defining a pubertal GnRH test (96% sensitivity, 100% specificity, no false positives) (5). Palmert's patient no. 15 had a peak LH-to-peak FSH ratio of 0.74, which is greater than 0.66. This patient also had a bone age advance of 3.6 years above CA and a height SDS for CA of −2.0. She had onset of menses at 8.8 yr. All of these things together would have suggested a compromised adult height outcome in this girl, and she probably would have been treated by some pediatric endocrinologists. However, without treatment, she also achieved a final height greater than her MPH and with a 0.2 SDS. The authors note some limitations of doing a questionnaire follow-up. An additional limitation is the accuracy of reported heights. If this reported height is accurate, this girl illustrates how unclear the assessment of the need for treatment can be.

Palmert *et al.* report that this groups of girls had good final height outcome on the average. However, not all girls achieved their MPH. Patients no. 11 and no. 14 achieved adult heights 10 cm and 12.6 cm below their MPH, respectively, and final height SDS of −1.9. Neither of these girls had peak LH levels over 15 IU/L or peak LH-to-peak FSH ratios over 0.66, so by Palmert's or our criteria would not have been treated. They did have significant advancement of BA, and they were two of the four girls who had measurable nocturnal LH pulses. These two girls again illustrate the complexity of distinguishing who needs treatment. Similar girls should undergo repeat evaluation periodically, watching for rate of pubertal progression, changes in predicted height, and determination if they meet biochemical criterion for treatment, which might improve their adult height outcome.

Neely *et al.* (8) studied 49 girls with clinical signs of true precocious puberty, and report that a baseline LH of more than 0.3 IU/L or a GnRH-stimulated LH peak of more than 5 IU/L (by the newer ICMA using World Health Organization 2nd International Standard, Human Pituitary LH 80/522) may be diagnostic of precocious puberty (7, 8). A few girls with true precocious puberty were still missed using these criteria. As stated by Palmert *et al.*, more studies with the newer assays may improve our definition of pubertal HPGA activity.

Estradiol levels have not been reliable for the diagnosis of precocious puberty. While some girls present the obviously pubertal estradiol levels, many girls present with estradiol levels below the detection limit of available RIAs, as in the girls reported by Palmert *et al.* We are investigating the potential usefulness of an ultrasensitive estradiol assay in the evaluation of precocious puberty (9, 10).

Do all children with true idiopathic precocious puberty need treatment?

Fontoura *et al.* (11) described a slowly progressive form of precocious puberty, in which pubertal development began

early but progressed slowly. They described 15 girls with clinical signs of precocious puberty before age 8 yr, but with BA advance less than 2 yr above CA. The girls were not treated and maintained predicted height over 2 yr of follow-up. They compared this group to another 19 girls with precocious puberty and BA advance greater than 2 yr above CA. The second group had lower predicted heights at onset and were treated. The untreated group had lower peak LH levels than the treated group. Because the second group was treated, we do not know if all of them would have progressed rapidly. Ten of the 19 had peak LH levels less than 15 IU/L. Again, the conclusion is that not all girls need treatment, but it cannot be concluded that the degree of BA advance can always distinguish which cases of puberty should be treated. Thirteen of 20 patients described by Palmert *et al.* had BA advance of more than 2 yr.

Kreiter *et al.* (12) described 7 girls with precocious puberty in whom predicted adult height was maintained over 2 yr of follow-up without treatment. They treated 14 girls with precocious puberty who had a loss in predicted height of at least 5 cm by two BA determinations at least 5 months apart or a predicted height less than 152.5 cm. Seven girls who did not meet these criteria were not treated. The groups did not differ in terms of gonadotropin testing, although individual test results were not given. Both groups had improvement in predicted height over the two yr. For comparison, note that 2 of the girls in the Palmert *et al.* study achieved final heights of less than 152.5 cm, a criterion Kreiter *et al.* would have used to initiate treatment.

Who should be treated?

Any girl with precocious physical signs of puberty, significantly advanced BA, decreased predicted height, and a pubertal response to gonadotropin testing should be treated with GnRH agonists to suppress pubertal progression and improve adult height. The problem remains that each of these variables (age of appropriate puberty, definition of significant BA advance, definition of decreased predicted height, and definition of a pubertal response to gonadotropin testing) is still not well defined and is approached differently by various investigators. There are many girls with an unequivocal evaluation who deserve treatment. It is the girls with a questionable evaluation of one or more of the above variables who need close attention and awareness by the clinician that treatment is not always necessary. No one has yet defined absolute criteria for determining who will benefit from treatment. Follow-up is extremely important in all girls, as it may become clear over time who needs treatment. Some estimate of adult height seems to be the most important predictor as reported by Fontoura *et al.* (11) and Kreiter *et al.* (12). The girls in the Palmert *et al.* study were selected by gonadotropin testing alone. All girls who are not treated need follow-up to evaluate pubertal progression, predicted height, pubertal gonadotropin levels, and possible benefit from treatment. Girls with true precocious puberty will continue to progress rapidly through puberty, so that repeat physical examinations will raise the suspicion of who needs repeat gonadotropin testing and possible treatment. Girls who don't need treatment will progress slowly or will be unsustained as described in this months' report by Palmert *et al.* Because it is important to treat girls with an unequivocal evaluation, it will be difficult to obtain absolute criteria for treatment at this point, as there will be no true comparison of untreated girls with more advanced bone age or more decreased predicted height. However, more studies should be done to try to distinguish what criteria to use. Palmert *et al.* report follow-up in girls who have achieved final height. Longer follow-up, including final height information in the other untreated series (11,12), may also help define criteria for treatment.

What can we conclude?

Our definition of precocious puberty is still being clarified, both from the perspective of age of physical changes and interpretation of gonadotropin levels. In addition, not all children with apparently true precocious puberty need medical intervention. Palmert *et al.* have described a group of girls who have the appropriate physical characteristics of precocious puberty, some with advanced bone maturation and some without, but none with biochemical evidence of pubertal HPGA activity, most of whom clearly did not require treatment. In addition, others have used BA advance criteria (11) or predicted height prognosis (12) to determine who to treat, even when girls fit a biochemical definition of precocious puberty, and have similarly shown that not all girls require treatment.

None of the untreated girls described by Fontoura (11), Kreiter (12), or Palmert *et al.* (1) had rapid progression of their puberty. In cases of possible precocious puberty that are equivocal (CA between 5–8 yr, BA not as advanced, predicted height still close to MPH, and/or GnRH testing unclear), it is important to obtain adequate follow-up including careful examination of the rate of progression of physical changes, linear growth, bone maturation, estimates of adult height, and stimulated gonadotropin levels, to determine which girls need treatment. More studies with the newer more sensitive gonadotropin assays and possibly studies with more sensitive estradiol assays are needed to determine if we can more accurately define puberty and to determine which children will benefit from treatment.

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