0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(8):3644–3650

doi: 10.1210/jc.2003-031532

EXTENSIVE PERSONAL EXPERIENCE

Clinical Characteristics of 104 Children Referred for Evaluation of Precocious Puberty

PAUL KAPLOWITZ

Department of Endocrinology, Children's National Medical Center, Washington, D.C. 20010

There is controversy over the age of onset of puberty in normal children and the risk of missing pathology if the recently proposed revised age guidelines for referring patients are followed. However, there is little recently published information on the frequency of different diagnoses in children referred for signs of early puberty. The purposes of this study were 1) to analyze the spectrum of diagnoses made in a consecutive group of children referred to a single clinician for signs of early puberty; 2) to see whether certain patient groups were more likely to be obese; and 3) to estimate the incidence of endocrine pathology in this sample.

The charts of all children referred to the author for evaluation of signs of early puberty between October 1999 and October 2002 were reviewed. Criteria were developed to assign patients to one of seven diagnostic categories based on age, growth, and clinical findings, and differences from the population mean for height and percentage of ideal body weight in the different groups were determined.

Most of the patients referred (87%) were female, and the two most common diagnoses made were premature adrenarche (46%) and premature thelarche (18%). Only 9% (all girls) were thought to have true precocious puberty. Two conditions not well described in the literature, pubic hair of infancy and premature menses, were found in 8 and 5%, respectively. Patients with premature adrenarche were significantly taller and more overweight than the general population; a subgroup had evidence of accelerated growth and bone maturation but no worrisome endocrine findings. Acanthosis nigricans was found in 13% of the girls in this study, but the incidence of true endocrine pathology was very low.

The majority of children being referred for precocious puberty have benign normal variants, with a very low incidence of endocrine pathology. Most girls presenting with minimal breast or pubic hair development and normal growth velocity may be managed with observation and without a full endocrine evaluation. (*J Clin Endocrinol Metab* 89: 3644–3650, 2004)

RECENT STUDIES IN the United States have suggested that girls are starting puberty at an earlier age than they were 30–40 yr ago, and that a significant number already have breast or pubic hair development by age 8 (1, 2). One of these studies, based on 17,000 girls examined by clinicians in the Pediatric Research in Office Settings (PROS) network, led to a proposal to change the age at which signs of puberty are considered precocious, from age 8 to age 7 for white girls or age 6 for black girls (3). Further analysis of the PROS study data indicated that girls between the ages of 6 and 9 yr who had breast or pubic hair development had a significantly higher mean body mass index SD score than age- and race-matched girls with no signs of puberty (4). This supports a body of evidence suggesting that the increased prevalence of obesity could be a major cause of both earlier puberty and earlier adrenarche in girls.

Some have questioned the validity of the PROS study and whether puberty in girls is in fact starting earlier than in the past. They have warned that changing the guidelines for when puberty is precocious will result in missing serious pathology if physicians do not refer all girls aged 8 or under who have breast or pubic hair development (5). A recent study at one Midwestern pediatric endocrine clinic claimed that of 223 girls referred for precocious puberty between ages 7 and 8 (white girls) or 6 and 8 (black girls), 47% had true precocious puberty and 12% had "pathologic explanations for their sexual precocity," the most common of which was acanthosis nigricans (6).

The purpose of this study is to review the clinical data on all children referred to a single clinician for evaluation of signs of early puberty over a 3-yr period starting in October 1999, when the revised puberty guidelines appeared. Criteria based mainly on the age, clinical examination, and growth data were used to define seven diagnostic categories. The objectives of the review were: 1) to determine the relative frequencies of the different diagnoses made; 2) to compare the different diagnostic groups in terms of age, reason for referral, relative height, and percentage of ideal body weight (IBW); and 3) to try to define the incidence of "endocrine pathology" in this referred sample of children.

Patients and Methods

Charts of all 104 children referred to the author for evaluation of precocious puberty at the Virginia Commonwealth University School of Medicine in Richmond, Virginia between October 1999 and October 2002 were reviewed. Age, race, the reason(s) given by the parent for the referral, the availability of growth data covering the previous 6–12 months, the mother's age of menarche, the height and weight, the amount of glandular breast tissue (recorded as the diameter of the breast

Abbreviations: Ht SD, Height SD; IBW, ideal body weight; PA, premature adrenarche.

excluding fat tissue), the Tanner stage of breast and pubic hair, and the presence or absence of axillary odor and acanthosis nigricans were recorded. Because it was often difficult to determine when the breast tissue or pubic hair actually appeared, there was no attempt made to define the precise age of appearance of these signs. The presence of breast development was defined as at least 1.0 cm in diameter of palpable glandular tissue when held between the thumb and index finger. Heights were converted to height SD scores (Ht SD) and weights were converted to percentage of IBW using the GenenCalc program version 2.0 from Genentech (South San Francisco, CA).

The general criteria for deciding how much testing and follow-up each child needed were developed by the author over a period of 10–15 yr. If the child had only stage 2 pubic hair or breast development that had been present for at least 6 months, and no evidence of rapid growth in the past 12 months based on measurements provided by the referring physician, generally no testing was done. If there were no growth records but the height was 90th percentile or greater, or the child was below the 90th percentile but parents had noted an increase in growth rate, it was assumed that growth acceleration was likely. If the child presented with either more advanced pubic hair or breast development, or evidence suggesting growth acceleration, a bone age was ordered for height prediction. For patients with pubic hair only and rapid growth, dehydroepiandrosterone sulfate, testosterone, and 17-hydroxyprogesterone were ordered to exclude nonclassical congenital adrenal hyperplasia or a virilizing tumor. For girls older than 6 yr with rapid linear growth and breast development with or without pubic hair, random levels of LH, FSH, and estradiol were obtained if treatment was contemplated. During most of the period covered by this study, LH assays were done by an automated colorimetric assay system called Immuno 1 (Bayer HealthCare LLC, Diagnostics Division, Tarrytown, NY), with a sensitivity for LH of 0.3 IU/liter and for FSH of 0.1 IU/liter. For screening purposes, LH levels less than 0.3 were considered prepubertal, as described by Neely *et al.* (7), and levels more than 0.3 IU/liter were considered pubertal. Magnetic resonance images were not obtained unless there were central nervous system-related symptoms, due to the very low incidence of abnormal findings in 6- to 8-yr-old pubertal girls (8). Follow-up visits were scheduled when the diagnosis was not clear at the first visit or when the history and/or examination suggested rapid progression. Parents not given a follow-up appointment were told to schedule another appointment if the signs of puberty were increasing rapidly over the next 4–12 months or if rapid growth was found on a visit to their primary care physician, who was notified in writing of this recommendation. Thirty-two patients were asked to schedule a follow-up appointment, and 22 were seen a second time, including four who were not asked to return but whose parents needed reassurance. Thus, for the majority of children, the analysis is based on a single visit. However, using these criteria, no patients seen by the author during the 10 yr before this study period who were not scheduled for follow-up returned at a later time with findings indicating a different diagnosis than was initially made.

Clinical criteria

After review, each child was assigned a diagnosis based on the following clinical criteria.

Premature adrenarche (PA). Early appearance of pubic hair without breast development (girls) or enlargement of the penis or testes (boys). Although children with PA typically grow at a normal rate, rapid growth was noted often enough, as discussed below, that this finding did not exclude a diagnosis of PA.

Premature thelarche. Appearance of breast tissue (Tanner stage 2) in a girl under 3 yr of age without evidence of rapid progression over time and no evidence of a central nervous system problem.

True early or precocious puberty. Girls with progressive breast enlargement associated with rapid growth, documented either by previous measurements from the referring physician or a follow-up visit with the author.

Early breast development not defined. This category was used for girls who had appearance of breast tissue (unilateral or bilateral) after 3 yr of age, but at the time of the visit, it was at stage 2 and was not associated with rapid growth. Ultimately, girls in this group could be diagnosed as having either later-onset premature thelarche, slowly or nonprogressive precocious puberty, or very early true precocious puberty.

Pubic hair of infancy. Appearance of fine straight hair in the genital area in boys or girls in the first year of life without evidence of progression, enlargement of the penis or clitoris, or rapid growth. This was felt to be different from the vellus hair that is normally found in nongenital areas of the body because its distribution was limited to the genital area.

Premature menses. Occurrence of one or more episodes of vaginal bleeding in a girl with no breast development, and no abnormal physical findings, hormonal studies, or imaging findings.

No puberty. No breast tissue or pubic hair was detected on examination. Most of these were overweight girls who had what appeared to be breast tissue by inspection, but by palpation, the amount of glandular tissue was less than 1.0 cm.

Statistical methods

One-sample *t* tests were used to test whether the mean Ht SD was significantly different from 0, whether the mean percentage of IBW was different than 100%, and whether mean maternal age at menarche was different than 12.7. To test for significant differences in continuous variables between race, sex, and acanthosis nigricans for patients with PA, two-sample tests were calculated. The appropriate *t* test (equal variances *vs.* unequal variances) was chosen based on the result of an *F* test for equality of variances. To correct for multiple testing, a Bonferroni correction was used with statistical significance reported at $\alpha = 0.05/3 = 0.0167$. This correction was chosen because *t* tests were performed on three variables. All analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

Results

Diagnostic categories and reason for referral (Table 1)

Of the 104 children referred for signs of early puberty, 90 (87%) were female. The most common diagnosis made was

TABLE 1. Distribution of diagnoses in 104 patients referred for precocious puberty, selected patient characteristics, and reasons for referral

Diagnosis	N (%)	M/F	B/W	Mean age ± SD (yr)	% Referred for this problem			
					Breast	Pubic hair	Rapid growth	Body odor
Premature adrenarche	48 (46)	11/37	26/20[a]	7.1 ± 1.4	31	98	29	35
Premature thelarche	19 (18)	0/9	14/5	1.7 ± 0.8	100	0	5.3	0
True precocious puberty	9 (9)	0/9	3/5	7.7 ± 0.9	89	33	44	22
Early breast development	9 (9)	0/9	3/6	7.1 ± 1.0	89	44	11	22
Pubic hair of infancy	8 (8)	3/5	7/1	0.8 ± 0.2	0	100	0	0
Premature menses	5 (5)	0/5	5/0	6.4 ± 3.1	0	0	0	0
No puberty	6 (6)	0/6	3/3	5.1 ± 1.0	100	17	17	0

M, Male; F, female; B, black; W, white.
[a] Includes one Hispanic and one Indian child.

PA (46%), of which 77% were girls and over half were black. The age at time of referral varied from 1.5 to 10 yr, but 81% were between the ages of 6 and 9 at the time of their first visit. Pubic hair was one of the reasons for referral in all but one patient, but rapid growth, body odor, and breast tissue were each given as reasons for the visit in about one third of the cases. Of the 37 girls with PA, 15 (41%) were thought by the parent and/or referring physician to have breast tissue, which was found to be fat tissue when examined by palpation.

The second most common diagnosis was premature thelarche, found in 18% (21% of girls), 74% of whom were black; the mean age at first visit was 1.7 yr. All were referred because of the breast tissue; rapid growth was part of the reason for the visit in only one case. Two girls were thought to have pubic hair that proved to be very fine body hair in the genital area, similar to that seen in children categorized as having pubic hair of infancy.

A diagnosis of true early or precocious puberty was made in 9% of the cases at a mean age of 7.7 yr, older than for the other diagnoses. Seven of nine were between ages 7 and 8 yr at the time of the first visit, and all were referred because of concern about early breast development, except for one patient referred because of onset of menses at age 9. Rapid growth was a major concern in 44%, and a smaller proportion was concerned about pubic hair and body odor. The mean age for the early breast development-not-defined group was 7.1 yr, and reasons for referral were similar, except that fewer had a concern about rapid growth.

All children with pubic hair of infancy were referred because of the hair in the genital area at a mean age of 0.8 yr. Mean age at referral for the five girls with premature menses was 6.4 yr; four of five were 7–8.5 yr old and one was 10 months old. Three of the five had had a single episode of vaginal bleeding lasting 2–6 d, one had two episodes 1 month apart lasting 2 d, and one had two episodes 3 wk apart lasting 1 d. LH was determined in three of five and was 0.3 IU/liter or less; FSH was 1.9–3.6 IU/liter. Three of these patients had a normal pelvic ultrasound, and the other two did not undergo testing but the vaginal bleeding stopped after a single episode.

Growth parameters of children referred for early puberty (Table 2)

Previous growth records were requested on all children referred for early puberty, but they were received in only 61% of cases.

Linear growth. As expected, the girls with true precocious puberty were significantly taller than age-matched peers (mean Ht SD, 1.5 ± 0.9; $P = 0.001$). The same was true of children with PA (mean Ht SD, 1.2 ± 1.1; $P < 0.0001$) and the girls with early breast development not defined (mean Ht SD, 1.1 ± 1.2; $P = 0.01$). None of the other diagnostic subgroups were significantly taller than average for age.

Weight. When weight was expressed as percentage of IBW, the PA patients were on the average 23% overweight ($P < 0.0001$). The "no puberty" group was 30% overweight ($P = 0.002$), which is not surprising because excess fat was mistaken for breast tissue. The true precocious puberty and premature menses groups were overweight to a similar degree, but because of the large SD and smaller numbers, this was not statistically significant. In the true precocious puberty group, six of nine patients had an increased percentage of IBW of 119–200%, whereas three had a normal percentage of IBW of 93–99%. In contrast, children with premature thelarche and pubic hair of infancy were on the average very close to their IBWs.

Maternal age of menarche. To examine the possible contribution of genetic factors to signs of early puberty, the mean age of maternal menarche was compared for the different subgroups with the population mean of 12.7 yr. There was a trend for mothers of girls with true precocious puberty and premature menses to start their periods earlier, but due to the small numbers, the differences were not statistically significant.

Because the 48 patients with PA were on the average tall and overweight, this group was further analyzed to see whether any clinical information available predicted which children were taller or more overweight than the group as a whole. Boys were somewhat older at time of referral and less overweight than girls, but the differences were not statistically significant. Patients with Ht SD more than 2 (21% of the PA group) were not different from the rest of the group in age, race, or in percentage of IBW. It was noted that nine patients, all female, had acanthosis nigricans. When this subgroup was compared with the 28 girls without acanthosis nigricans, they were more likely to be black (89 *vs.* 43%), somewhat taller (mean Ht SD, 1.7 *vs.* 1.0), and considerably more overweight (160.9 *vs.* 114.5% of IBW; $P < 0.0001$).

Of the 10 patients with PA with height more than 2 SD, eight (17% of the total group; five girls and three boys) had previous growth data indicating accelerated growth during the year before referral. All had heights somewhat above the

TABLE 2. Growth and maternal menarche in different subgroups of children referred for precocious puberty

Diagnosis	N (%)	% With growth records (%)	Mean Ht SD	Mean % IBW	Mean maternal age of menarche
Premature adrenarche	48 (46)	62.5	1.2 ± 1.1[a]	122.9 ± 27[a]	12.2 ± 1.5
Premature thelarche	19 (18)	63.2	0.6 ± 1.3	101.2 ± 12	12.2 ± 1.4
True precocious puberty	9 (9)	55.6	1.5 ± 0.9[b]	126.9 ± 36	11.7 ± 1.8
Early breast development	9 (9)	33.3	1.1 ± 1.2[c]	115.3 ± 30	13.0 ± 1.1
Pubic hair of infancy	8 (8)	87.5	−0.04 ± 1	97.6 ± 7.2	13.7 ± 1.7
Premature menses	5 (5)	40	0.8 ± 0.7	129.6 ± 21	10.9 ± 1.3
No puberty	6 (6)	67	0.96 ± 1.2	130.7 ± 16[d]	12.5 ± 1.4

Versus population mean (Ht SD 0.0 or 100% IBW): [a] $P < 0.0001$; [b] $P = 0.0005$; [c] $P = 0.01$; [d] $P = 0.002$.

95th percentile by ages 4–6 yr, in most cases before the appearance of pubic hair, and all had at least one parent 3 in. or more above the adult mean. Three of the five girls but none of the three boys were overweight. Bone ages done on seven of the eight patients were all advanced by between 2 and 3 yr, but height for bone age was 50th–90th percentile, indicating that despite the advanced bone age, all had a predicted adult height within the normal range. Studies to screen for pathological overproduction of androgens due to a tumor or nonclassical congenital adrenal hyperplasia (dehydroepiandrosterone sulfate, testosterone, and 17-hydroxyprogesterone) were normal in all cases. Six of the eight were seen in follow-up 4–6 months later and accelerated growth rates (7–11 cm/yr) were confirmed, but none exhibited new physical findings or a detectable increase in the amount of pubic hair.

Incidence of endocrine pathology

Deciding what constitutes endocrine pathology is difficult, but the definition proposed here is to include in this category any patient who was found to have a condition that required either medical or surgical treatment to slow or stop the progression of puberty. Of the 104 referrals made for early puberty, one patient proved to have a surgical condition with endocrine implications, a 7-yr-old overweight white female referred for breast and pubic hair development, but who had no definite breast tissue. Three months later, because of loss of temporal vision, a magnetic resonance image showed what proved to be a large hypothalamic astrocytoma; LH and FSH were unmeasurable. Postoperatively, hypernatremia with dilute urine was noted, consistent with diabetes insipidus, and the mother then reported a 2-yr history of polyuria and polydipsia, which had not been mentioned at the initial visit. One year later, breast development was clearly progressing and her LH, FSH, and estradiol levels were in the pubertal range.

Of the nine patients who were judged to have progressive precocious puberty, treatment with Lupron (leuprolide acetate; TAP Pharmaceutical Products, Lake Forest, IL) was recommended for three of them. Two of them presented at age 7–7.5 yr with stage 3 breast development and growth acceleration but normal predicted height, and treatment was suggested because of the likelihood of menarche before age 9. Another patient presented at age 9 after her first period, and the mother requested treatment to prevent further menses. The other six children were not offered treatment because at the time of their initial visit at 7.5–8.5 yr of age, their breast development had not progressed beyond stage 2, and it was estimated that menarche would start after age 9, and the parents felt they could manage it. Most were seen a second time, and the progression of puberty was not rapid, so no further follow-up was recommended.

Twelve (13.3%) of the girls in this review (nine with PA and three others) had acanthosis nigricans, but whether this should be considered endocrine pathology will be discussed below. About 25% of the patients were scheduled for follow-up and 20% were actually seen a second time, including some who were not scheduled but whose parents or pediatrician needed reassurance. When this review was concluded, between 6 months and 3.5 yr had passed since the initial visit, but none of the patients with PA, premature thelarche, or early breast development not defined either called to report or returned with new findings that altered the initial clinical impression. One girl initially diagnosed with pubic hair of infancy at age 10 months was seen back for follow-up at age 4 yr. Her growth was normal and the pubic hair had slowly become longer and coarser, attaining an appearance more typical of PA.

Discussion

Of the 104 children who were referred to the author for evaluation of precocious puberty, 78% had benign diagnoses that can be considered variants of normal (PA, premature thelarche, pubic hair of infancy, no puberty with fat simulating breasts) and for which no treatment is indicated. Five percent had premature menses, which is poorly understood but generally self-limited. No patient in this group had peripheral precocious puberty, a group of rare but potentially serious conditions that include adrenal and ovarian tumors, congenital adrenal hyperplasia, and McCune-Albright syndrome. Only nine patients had progressive early or precocious puberty. However, eight patients were age 7 yr or older at the time of their initial visit, none had a predicted height of less than 62 in., and only three were treated with GnRH analogs as noted above. Another nine patients had early breast development starting at between 5.5 and 8 yr, which did not appear to be progressive. Some of these patients likely have premature thelarche starting at a later age than usual, and others may have unsustained or slowly progressive precocious puberty, a variant which does not require treatment unless progression becomes rapid (9). Thus, only 4% of this group of patients ultimately required endocrine or surgical therapy.

The most comparable previous study of children referred for precocious puberty included 213 patients (197 girls and 16 boys), seen from 1975–1990 at Middlesex Hospital in the United Kingdom (10). Forty percent were girls with idiopathic true precocious puberty, 25% had premature thelarche, and 14% had thelarche variant, similar to the early breast development category in the present study. It is striking that only 10% of the girls (but 50% of boys) were diagnosed with PA; this condition is thus far more common in U.S. girls now than in British girls 15–25 yr ago and has replaced true precocious puberty as the major reason for referral of girls with early puberty. There were 10 patients (5%) with true precocious puberty due to intracranial pathology and five (2%) with peripheral precocious puberty; neither group was represented in the current study. Whether these differences reflect changes over time in the underlying frequency of these conditions or differences in the criteria for referral between the Middlesex area of United Kingdom and the area around Richmond, Virginia is not known.

Comparison of Ht SD and percentage of IBW in the different subgroups reveals some important differences. It was expected that girls with true precocious puberty would be tall as a group, because they all had evidence of accelerated growth. The finding of increased weight in six of nine subjects is consistent with evidence that increased body fat may

contribute to earlier puberty in some girls (4, 11). Patients with PA (both boys and girls) were also tall for their age (mean Ht SD, 1.2), and they were on the average 23% overweight, with girls being more overweight than boys. The findings support the concept that adrenal androgens at levels seen in PA can cause increased linear growth and also implicate increased body fat as a risk factor for early development of pubic hair, as suggested in a previous cross-sectional study (4). Because some prepubertal girls with PA have evidence of insulin resistance (12), one can speculate that the higher insulin levels associated with obesity may stimulate adrenal enzymes involved in adrenal androgen production. The presence of acanthosis nigricans, a marker of insulin resistance, in a subset of girls with PA who were particularly obese underscores the possible association of elevated insulin levels and increased adrenal androgens. Such girls have been found to be at an increased risk for developing polycystic ovary disease and metabolic syndrome in their adolescent years (13), suggesting that they may need long-term follow-up.

Among the 48 patients with PA, eight (five girls and three boys) who had a Ht SD more than 2.5 had evidence of growth acceleration based on measurements provided by referring physician and confirmed in most cases at a follow-up visit. Physical examinations showed only pubic hair with no other signs of androgen excess such as phallic enlargement or acne; baseline hormone levels were normal in all cases; and bone ages were advanced but appropriate for their height ages. Others have noted that in PA, growth velocity may be increased, which is associated with bone age advancement of 1–2 yr, which correlates with increased height (14). One report found a significant increase in Ht SD (0.9 *vs.* 1.2 in the present study) and bone age SD (mean 1.5) at 1–2 yr after the onset of pubic hair, but height and bone age advancement declined between yr 3–6 of follow-up (15). Thus, some children with PA may be predisposed to have rapid growth when exposed to the modestly increased levels of adrenal androgens characteristic of adrenarche. Long-term follow-up data on patients with PA are reassuring, because these children tend to have the onset of puberty at the early end of the normal range and achieve final heights appropriate for their genetic potential (15).

In contrast, children with premature thelarche and pubic hair of infancy were, as a group, of normal height and weight. This suggests that the underlying cause of these two conditions may be quite different from true precocious puberty and PA, respectively. It has been proposed that premature thelarche represents the earliest stage in a continuum of activation of the hypothalamic-pituitary-gonadal axis, which can include slowly progressive and classic precocious puberty (16, 17). However, a long-term follow-up study of 42 girls from Italy diagnosed with premature thelarche before age 3 yr indicated that the age of menarche was consistent with the maternal age of menarche and that mean final height was actually slightly higher than the genetic target height (18). None of the premature thelarche patients in the current study appeared to have progressed to true precocious puberty, and the author has never in 20 yr seen a girl initially thought to have premature thelarche presenting at 3 yr of age or less who turned out to have true precocious puberty.

There is little known about the cause or natural history of pubic hair of infancy. Diamond *et al.* (19) in 1989 described six healthy boys aged 4–8 months with hair on the scrotum, which disappeared over time, but no other signs of androgen excess. Adams *et al.* (20) described three girls with labial hair in infancy, in whom testosterone levels were all appropriately low; ACTH testing was normal in two and possibly indicative of deficiency of the adrenal enzyme 3β-hydroxysteroid dehydrogenase in one. The fact that over a 3-yr period eight infants were seen with fine labial or scrotal hair suggests this condition is becoming more common. Because none of the cases had growth acceleration or any other signs of androgen excess, hormonal studies were not routinely obtained. The cases seen in follow-up had no progression of findings, except for the girl seen again 3 yr later who had still normal growth and an examination consistent with typical PA. Until we learn more about this probably benign entity, it seems appropriate to monitor the progress of these infants with a minimum of hormone testing, unless there is growth acceleration and/or other evidence of increased androgen production.

Five girls were given a diagnosis of premature menses, which has been described before but is not considered common (21). Some have found elevated estradiol levels with prepubertal gonadotropins and have proposed that these levels are due to instability of the hypothalamic-pituitary-gonadal axis (22), although the underlying cause is still obscure. Because bleeding was intermittent and never present at the time of evaluation, one needs to rely on the parents' report that what they saw was blood and that it came from the vagina and not the rectum. The possibility of sexual abuse or insertion of a foreign body into the vagina needs to be considered, particularly if there are signs of trauma or infection. The fact that in this series there were five cases in 3 yr, and that others are seeing this condition more frequently (communications posted on the pediatric endocrinology electronic bulletin board), suggests that it may be becoming more common. Although these patients need referral and evaluation, if nothing abnormal is found, the parents can be advised based on the literature that the bleeding will likely stop after a few episodes, as occurred in all five patients in this series. A follow-up study of 12 patients with this entity found that all had menarche between ages 10.5 and 14 yr and were having regular monthly menses (22).

Precocious puberty in boys is known to be much less common than in girls and is more likely to be associated with brain tumors or other central nervous system abnormalities (10). However, over a 3-yr period, none of the 14 boys referred for early puberty had the increased penile or testicular size that would have suggested either true or peripheral precocious puberty. Three were under 1 yr of age and were considered to have pubic hair of infancy, and the other 11 had PA. The most recent data on the timing of puberty in boys come from the National Health and Nutrition Examination Survey III study of 1988–1994 (23), in which 15% of 8- to 9-yr-olds were reported to have stage 2 genital development. This very high figure was likely due to misclassification of early genital development, which is somewhat subjective, because neither this investigator nor others have noted an increase in referral of boys with true precocious puberty. The

prevalence of pubic hair in 8- to 9-yr-olds, which is a more objective finding, was 5.3% in black, 2.7% in Hispanic, and 0% in white boys. Although the incidence of pathology in boys referred for early puberty in this study was zero, it seems reasonable to continue to evaluate boys who have the appearance of any signs of puberty, including pubic hair, before age 9.

Two recent studies have documented that about 30% of black girls and about 7% of white girls already have pubic hair by age 8–9 yr (1, 2). Thus, the old guidelines, which suggest that all girls who have pubic hair by this age need an endocrine evaluation, appear to be resulting in excessive referrals of normal children. Following the revised guidelines (3), which recommend referral of white girls with pubic hair before age 7 and black girls with pubic hair before age 6, would decrease the number of referrals for pubic hair with only a small risk of missing pathology. In the current study, of the 37 girls with PA, only 10 would have needed referral according to the revised age guidelines, and another five because of rapid growth. Primary care physicians need to learn to assess breast tissue by palpation, not just inspection, particularly in overweight girls, to distinguish it from fat tissue. In 31% of the children with PA (41% of the girls), concern about breast development was part of the reason for the referral. Another five children were thought to have only breast tissue, which proved to be fat tissue. Regardless of whether they are referred or not, the need for regularly measuring and plotting children with signs of early puberty is clear. In the current study, only 61% of referred children had growth records transmitted to the specialist. Having this critical information will help the primary care physician decide which children need to be referred most urgently and aid endocrinologists in deciding at the first visit if a more complete endocrine evaluation is needed.

There is concern among some pediatric endocrinologists that failure to refer all children with any signs of puberty before age 8 will result in missing important pathology (5). The authors of a recent study of 6- to 8-yr-old girls referred for early puberty (6) concluded that significant endocrine diagnoses were made in 26 (12.3%) of 212 girls, of whom 15 (58%) had acanthosis nigricans. This skin change commonly seen in obese patients, more frequently in black than in white subjects, has been thought to reflect insulin resistance, but two recent pediatric studies (24, 25) found that it was a better marker for obesity than for hyperinsulinemia. If we define endocrine pathology as a condition that requires specific medical or surgical treatment, it is not clear that acanthosis nigricans should be included, because counseling on lifestyle changes is currently all that we have to offer such patients. However, because these children have an increased risk for developing type 2 diabetes and features of the metabolic syndrome, it is appropriate for physicians to pay attention to this finding, screen periodically for type 2 diabetes, and at least refer them for nutritional counseling, whether or not they have breast or pubic hair development. The second most common endocrine diagnosis was hypothyroidism (four patients), but no details were provided. Severe and long-standing hypothyroidism has in rare cases been associated with precocious puberty, possibly due to an FSH-like effect of greatly elevated TSH levels (26). Quite possibly, those four patients had subclinical hypothyroidism, a common problem which has not been associated with precocious puberty and for which the benefits of treatment are controversial (27). Thus, the true prevalence of endocrine pathology in their study is much lower than 12%. The authors also claimed that 35% of their sample had diminished growth potential due to advanced bone age; in this study, bone age was done selectively when there was rapid progression of findings and/or growth acceleration, and in no case was bone age more advanced than height age.

One child in the current study proved to have a central nervous system tumor after being seen at age 7 for pubic hair. Hypothalamic astrocytoma is a tumor that has been associated with true precocious puberty, but at the time the tumor was diagnosed, the child did not have breast development and had undetectable levels of LH until 9 months after surgery. Because early appearance of pubic hair in girls has not been associated with brain tumors, in this case, its association with the astrocytoma may have been coincidental. In addition, the loss of peripheral vision with a 2-yr history of polyuria and polydipsia, ultimately found to be due to diabetes insipidus, should have resulted in a referral to a pediatric endocrinologist even before the pubic hair was noted. There were also three children in this study with idiopathic central precocious puberty that was progressing rapidly enough that treatment was recommended to prevent (two cases) or stop (one case) early menses.

In summary, a retrospective review of 104 children referred over a 3-yr period to a single clinician for signs of early puberty revealed a low incidence of endocrine pathology and a high proportion of children with common benign variants of normal. It is suggested that most patients with Tanner stage 2 breast or pubic hair development can be evaluated with only a history, physical examination, and review of the growth chart, without the need for hormonal studies and an estimate of bone age, provided that growth is normal. Additional time for observation will identify the occasional child with growth acceleration and rapid progression of breast, pubic hair, or genital development, who is much more likely to benefit from a full endocrine evaluation.

Acknowledgments

Received September 3, 2003. Accepted April 12, 2004.

Address all correspondence and requests for reprints to: Paul Kaplowitz, M.D., Ph.D., 111 Michigan Avenue NW, Washington, D.C. 20010. E-mail: pkaplowi@cnmc.org.

References

1. **Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM** 1997 Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatrics Research in Office Settings network. Pediatrics 99:505–512
2. **Wu T, Mendola P, Buck GM** 2002 Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988–1994. Pediatrics 110:752–757
3. **Kaplowitz PB, Oberfield SE** 1999 Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. Pediatrics 104:936–941
4. **Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME** 2001 Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics 108:347–353

5. **Rosenfield RL, Bachrach LK, Chernausek SD, Gertner JM, Gottschalk M, Hardin DS, Pescovitz OH, Saenger P** 2000 Current age of onset of puberty. Pediatrics 105:115–116
6. **Midyett LK, Moore WV, Jacobson JD** 2003 Are pubertal changes in girls before age 8 benign? Pediatrics 111:47–51
7. **Neely EK, Wilson DM, Lee PA, Stene M, Hintz RL** 1995 Spontaneous serum gonadotropin concentrations in the evaluation of precocious puberty. J Pediatr 127:47–52
8. **Chalumeau M, Chemaitilly W, Trivin C, Adan L, Breart G, Brauner R** 2002 Central precocious puberty in girls: an evidence-based diagnosis tree to predict central nervous system abnormalities. Pediatrics 109:61–67
9. **Palmert MR, Malin HV, Boepple PA** 1999 Unsustained or slowly progressive puberty in young girls: initial presentation and long-term follow-up of 20 untreated patients. J Clin Endocrinol Metab 84:415–423
10. **Bridges NA, Christopher JA, Hindmarsh PC, Brook CGD** 1994 Sexual precocity: sex incidence and aetiology. Arch Dis Child 70:118–120
11. **Davison KK, Susman EJ, Birch LL** 2003 Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. Pediatrics 111:815–821
12. **Dimartino-Nardi J** 1999 Premature adrenarche: findings in prepubertal African-American and Caribbean-Hispanic girls. Acta Paediatr Suppl 88:67–72
13. **Ibanez L, Potau N, Virdis R, Zampolli M, Terzi C, Gussinye M, Carrascosa A, Vicens-Calvet E** 1993 Postpubertal outcome in girls diagnosed of premature pubarche in childhood: increased frequency of functional ovarian hyperandrogenism. J Clin Endocrinol Metab 76:1599–1603
14. **Reiter EO, Saenger P** 1997 Premature adrenarche. Endocrinologist 7:85–88
15. **Ibanez L, Virdis R, Potau N, Zampolli M, Ghizzoni L, Albisu A, Carrascosa A, Bernasconi S, Vicens-Calvet E** 1992 Natural history of premature pubarche: an auxological study. J Clin Endocrinol Metab 74:254–257
16. **Pescovitz OH, Hench KD, Barnes KM, Loriaux DL, Cutler GB** 1988 Premature thelarche and central precocious puberty: the relationship between clinical presentation and the gonadotropin response to luteinizing hormone-releasing hormone. J Clin Endocrinol Metab 67:474–479
17. **Ilicki A, Prager Lewin R, Kauli R, Kaufman H, Schachter A, Laron Z** 1984 Premature thelarche–natural history and sex hormone secretion in 68 girls. Acta Paediatr Scand 73:756–762
18. **Salardi S, Cacciari E, Mainetti B, Mazzanti L, Pirazzoli P** 1998 Outcome of premature thelarche: relation to puberty and final height. Arch Dis Child 79:173–174
19. **Diamond FB, Shulman DI, Root AW** 1989 Scrotal hair in infancy. J Pediatr 114:999–1001
20. **Adams DM, Young PC, Copeland KC** 1992 Pubic hair in infancy. Am J Dis Child 146:149–151
21. **Murram D, Dewhurst J, Grant DB** 1983 Premature menarche: a follow-up study. Arch Dis Child 58:142–143
22. **Blanco-Garcia M, Evain-Brion D, Roger D, Job M** 1985 Isolated menses in prepubertal girls. Pediatrics 76:43–47
23. **Herman-Giddens ME, Wang L, Koch G** 2001 Secondary sexual characteristics in boys: estimates from the National Health and Nutrition Examination Survey III, 1988–1994. Arch Pediatr Adolesc Med 155:1022–1028
24. **Nguyen TT, Keil MF, Russell DL, Pathomvanich A, Uwaifo GI, Sebring NG, Reynolds JC, Yanovski JA** 2001 Relation of acanthosis nigricans to hyperinsulinemia and insulin sensitivity in overweight African American and white children. J Pediatr 138:474–480
25. **Hirschler V, Aranda C, Oneto A, Gonzalez C, Jadzinsky M** 2002 Is acanthosis nigricans a marker of insulin resistance in obese children? Diabetes Care 25:2353
26. **Anasti JN, Flack MR, Froehlick J, Nelson LM, Nisula BC** 1995 A potential novel mechanism for precocious puberty in juvenile hypothyroidism. J Clin Endocrinol Metab 80:276–279
27. **Chu JW, Crapo LM** 2001 The treatment of subclinical hypothyroidism is seldom necessary. J Clin Endocrinol Metab 86:4591–4599

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.