Interrelationship of Extent of Precocious Adrenarche in Appropriate for Gestational Age Girls with Clinical Outcome

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Objective To assess the interrelationship between extent of adrenarche at presentation in girls with precocious adrenarche (PA) born appropriate for gestational age and their growth pattern, pubertal course and adult height.

Study design We reviewed clinical and laboratory data from medical charts of 85 girls with PA aged 5.0 to 8.8 years at referral, stratified in 3 subgroups according to bone age (BA) minus chronological age (CA) ≤0 years; 0 <BA minus CA <1 year; BA minus CA >1 year.

Results Extent of pubarche and dehydroepiandrosterone-sulfate levels were greatest in the BA−CA >1 subgroup ($P = .02$, $P = .008$, respectively), who also were taller at diagnosis ($P = .002$) and during childhood ($P = .01$). In all subgroups, pubertal onset was within normal range; menarche occurred earlier than in control subjects ($P < .02$); all attained adult height within their mid-parental height range. Predicted adult height was overestimated in girls with BA ≤CA ($P = .04$) and underestimated with BA−CA >1 ($P < .001$).

Conclusions Although a more pronounced adrenarche and BA advancement at diagnosis in girls with PA born appropriate for gestational age had an impact on their pre-pubertal growth pattern, it was not associated with early and rapid progression of puberty or reduced adult height. This reassuring clinical course indicates that PA is a benign condition, irrespective of the extent of adrenarche at presentation. Adult height prediction is unreliable in PA. *(J Pediatr 2011;■:■-■).*

Precocious pubarche refers to the isolated appearance of sexual hair with no evidence of gonadarche, frank virilization, or both before the age of 8 years in girls when androgen-producing tumors, steroidogenic enzyme defects, and central puberty have been excluded.[1] It usually occurs after age 4 years and can be associated with axillary hair, pre-acne or acne, and body odor. Bone elongation and maturation rates tend to be higher than average, as reflected by increased growth velocity and bone age (BA) advancement. In most cases, precocious pubarche is related to precocious adrenarche (PA), the non-pathological premature secretion of adrenal androgens. The biochemical hallmark of PA is elevation in serum concentrations of dehydroepiandrosterone-sulfate (DHEA-S).[2] Although it has been suggested that PA may stem from either a persistent fetal adrenal zone or premature development of the adrenal zona reticularis,[2] the underlying cause of adrenal androgens oversecretion in PA remains largely unknown.

PA is generally regarded as a benign condition characterized by a slow progression of bone maturation, lack of virilization, lack of gonadotrophin pulses, normal onset and progression of sexual development, and uncompromised adult height.[3,4]

However, previous studies have reported that in girls born small for gestational age (SGA) and in obese girls, PA was associated with an earlier age of menarche and a tendency toward metabolic syndrome, polycystic ovary syndrome, and insulin resistance at young adulthood.[5-8]

PA in girls born appropriate for gestational age (AGA) is characterized by a broad spectrum of clinical manifestations.

However, the interrelationship between extent of PA at presentation and the growth pattern, pubertal course, and final height has not been sufficiently addressed in earlier studies. Furthermore, most longitudinal studies of girls with PA were carried out in those born SGA.

The objective of this retrospective study was to assess whether the extent of PA at diagnosis influences the growth pattern, timing of puberty, age at menarche, and adult stature in girls born AGA.

17OHP	17 hydroxyprogesterone	Ht	Height
Δ4A	Androstenedione	IGF	Insulin-like growth factor
AGA	Appropriate for gestational age	MPHt	Mid-parental Ht
BA	Bone age	PA	Precocious adrenarche
BMI	Body mass index	PAHt	Predicted adult height
CA	Chronological age	SGA	Small for gestational age
DHEA-S	Dehydroepiandrosterone-sulfate	Wt	Weight
GnRHa	Gonadotropin-releasing hormone analogue		

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The authors declare no conflicts of interest.

 10.1016/j.jpeds.2011.08.009

Methods

The medical files of Israeli girls born AGA between the years 1982 and 1992 and attending our endocrinology clinic because of PA were reviewed. All were observed from early childhood through adolescence until young adulthood. All girls met these inclusion criteria: appearance of pubic or axillary hair before age 8 years with no signs of gonadarche (breast development stage 1 according to Tanner)[9] and available data on age at menarche and adult height. Excluded from the study were girls born SGA and girls with chronic disease, genetic syndromes, bone dysplasia, congenital adrenal hyperplasia, and other endocrine abnormalities.

The study cohort was stratified in 3 subgroups according to the degree of BA advancement at diagnosis: no advancement, BA minus chronological age (CA) ≤0 years; mild advancement, 0< BA minus CA <1 year; and moderate advancement, BA minus CA >1 year.

Twelve girls who had psychosocial difficulties in coping with the state of relatively early puberty received gonadotropin-releasing hormone analogue (GnRHa) therapy and therefore were not included in the analysis of pubertal course, age at menarche, and auxological measures at young adulthood.

Serving as control subjects for age at menarche were 106 women matched for age and year of birth to the studied cohort. These healthy young women were mothers of children observed in our clinic because of congenital hypothyroidism. The mother's medical condition and age at menarche were obtained from the child's medical file.

The study protocol was approved by the institutional review board.

Information collected from medical files included: perinatal history (duration of pregnancy, birth weight), parental height and patients' data including CA, BA, height (Ht) and weight (Wt) at diagnosis, at onset of puberty, at menarche, and at adult height. Secondary sexual characteristics—adrenarche (pubic hair, axillary hair, presence of acne) and gonadarche—were assessed according to Tanner[9] at referral, onset of puberty, and at menarche. The clinical evaluation in all cases was performed by pediatric endocrinologists at the Schneider Children's Medical Center.

Anthropometric measurements were obtained at 6- to 12-month intervals. Ht was measured with a Harpenden stadiometer (Holtain Ltd, Crosswell, United Kingdom). Wt was expressed as body mass index (BMI; Wt in kilograms/Ht in meters squared). Ht, Wt, and BMI were assessed as Ht, Wt, and BMI SDS.

Ht SDS, Wt SDS, and BMI SDS were calculated according to the recommendations of the Centers for Disease Control.[10] The mid-parental Ht (MPHt) was calculated according to Tanner et al.[11] The MPHt range was defined as MPHt ± 2.5cm (1 SD).[12] Pre-pubertal and pubertal stages were graded with Tanner scores for breast development.[9] Onset of puberty was defined as genitalia Tanner stage 2, associated with appearance of breast buds. End of puberty was considered to have occurred when pubertal signs corresponded to Tanner stage 5: breast development stage 5 with menarche associated with pubic hair stage 5.[9] Duration of puberty was estimated by the duration of transition from Tanner stage 2 to 5. A duration <2.5 years was considered fast puberty.[13] Total pubertal growth was calculated as the difference between height at completion and at onset of puberty. Adult height was defined by a height velocity <2.5 cm/year and by evidence of epiphyseal closure on radiography of the hand, defined as BA >15 years. Skeletal maturation was assessed by senior pediatric endocrinologists on the basis of roentgenograms of the left hand and wrist, evaluated according to Greulich and Pyle, with BA SDS calculated accordingly.[14] Predicted adult height (PAHt) was calculated according to the tables of Bailey and Pinneau.[15]

Laboratory Assessments

Hormonal evaluation included basal androgen profile (DHEA-S, androstenedione [Δ4A], testosterone, and comps when indicated), basal and post-corticotropin (0.25 mg, IV Synacthen, Ciba-Geigy, Basel, Switzerland) stimulated 17 hydroxyprogesterone (17OHP) and cortisol to exclude an adrenal enzymatic defect. All hormonal analyses were performed in the endocrine laboratory of our hospital with commercial kits: 17OHP, testosterone (Coat a Count Kit, DPC, Los Angeles, California); Δ4A - Double Antibody Kit (DSL, Webster, Texas); cortisol DHEA-S chemiluminescent enzyme immunoassay (DPC, Los Angeles, California).

Statistical Analysis

The data were analyzed with BMDP statistical software,[16] and the results are expressed as mean ± SD. Discrete variables were compared with Pearson χ^2 or Fisher exact test, as appropriate. Continuous variables were compared with ANOVA. ANOVA with repeated measures was applied to determine the effect of the "subgroup" (no BA advancement, mild BA advancement, and moderate BA advancement) on changes with "time" (at diagnosis, at onset of puberty, and at young adulthood). A P value <.05 was considered significant.

Results

Age at referral of the 85 studied girls ranged from 5.0 to 8.8 years, with no significant difference in mean CA of the 3 subgroups (**Table**). There was BA advancement in 67 girls (79%), which was mild in 36 (43%) and moderate in 31 (36%). In 18 girls (21%), BA corresponded to or was slightly less than CA.

The degree of pubarche at diagnosis differed: the pubic hair stage was significantly more advanced in the girls with moderately advanced BA than in girls with mild or no BA advancement ($P = .02$). The degree of axillary hair and the presence of acne was similar in the 3 subgroups. In the entire cohort, basal DHEA-S levels were in the early pubertal range,[17] but were significantly higher in girls with moderate BA advancement ($P = .008$). Corticotropin-stimulated 17OHP and basal Δ4A and testosterone were within the

Table. Clinical characteristics of girls with PA born AGA at diagnosis, at onset of puberty, and at young adulthood stratified according to degree of BA advancement

	Total	BA−CA <0	0 <BA−CA <1	BA−CA >1	*P* value
Number	85	18	36	31	
Birth data					
GA, wks	39.3 ± 2.2	39.0 ± 2.2	39.6 ± 2.3	39.0 ± 2.3	NS
Birth weight, g	3080 ± 550	2939 ± 680	3131 ± 530	3103 ± 500	NS
At diagnosis					
CA, years	7.4 ± 0.9	7.7 ± 0.7	7.2 ± 0.9	7.4 ± 1.1	NS
BA SDS	0.9 ± 1.0	−0.3 ± 0.5	0.7 ± 0.4	1.8 ± 0.8	<.001
Ht SDS	0.6 ± 0.9	0.1 ± 0.9	0.5 ± 0.7	0.9 ± 0.9	.002
BMI SDS	0.7 ± 1.1	0.4 ± 1.4	0.7 ± 1.1	0.9 ± 0.9	NS
Pubic hair					
Tanner 1	5 (5.8%)	1 (5.6%)	1 (2.8%)	3 (9.7%)	.02
Tanner 2	66 (77.7%)	16 (88.8%)	32 (88.8%)	18 (58%)	
Tanner 3	14 (16.5%)	1 (5.6%)	3 (8.4%)	10 (32.3%)	
Axillary hair					
Tanner 1	40 (47.0%)	10 (55.5%)	18 (50.0%)	12 (38.7%)	NS
Tanner 2	36 (42.3%)	7 (38.9%)	17 (47.2%)	12 (38.7%)	
Tanner 3	9 (10.7%)	1 (5.6%)	1 (2.8%)	7 (22.6%)	
Acne	20 (24.0%)	3 (16.7%)	7 (19.4%)	12 (38.7%)	NS
Peak 17OHP (n < 30 nmol/L)	8.8 ± 4.2	9.9 ± 5.0	8.8 ± 4.0	8.2 ± 4.0	NS
DHEA-S (n = 0.2-1.7 μmol/L)	2.5 ± 1.6	1.8 ± 0.8	2.2 ± 1.0	3.1 ± 2.2	.008
Δ4A (n = 0.6-2.4 nmol/L)	1.8 ± 1.1	1.4 ± 0.9	1.9 ± 1.0	2.0 ± 1.2	NS
At onset of puberty					
CA, years	9.5 ± 0.9	9.7 ± 0.9	9.6 ± 0.9	9.3 ± 0.9	NS
BA SDS	1.2 ± 1.0	0.1 ± 0.7	1.2 ± 1.0	1.7 ± 0.7	<.001
Ht SDS	0.6 ± 0.8	0.0 ± 0.9	0.5 ± 0.7	0.8 ± 0.8	.01
BMI SDS	0.7 ± 0.9	0.2 ± 1.0	0.8 ± 1.0	0.8 ± 0.8	NS
*At menarche					
CA, years	12.4 ± 1.2	12.4 ± 1.2	12.3 ± 1.0	12.4 ± 1.4	NS
Duration of puberty, years	2.9 ± 1.2	2.6 ± 0.6	2.8 ± 1.0	3.2 ± 1.5	NS
TPG, cm	22.8 ± 5.6	23.7 ± 4.9	22.2 ± 5.8	22.8 ± 6.0	NS
*At young adulthood					
Ht SDS	0.0 ± 0.9	−0.2 ± 0.8	−0.1 ± 0.9	0.3 ± 0.9	NS
BMI SDS	0.0 ± 0.9	−0.3 ± 0.9	0.1 ± 0.9	0.2 ± 0.9	NS

GA, gestational age; *TPG*, total pubertal growth; *NS*, not significant.
*Total of 73 patients.

reference range for age and the prepubertal stage,[17] with no significant differences in the 3 subgroups.

In the entire cohort, onset of puberty (breast development stage 2 according to Tanner) occurred within the normal age range, with no significant difference in the 3 subgroups (Table). Twelve girls (14%) received GnRHa therapy for 1.35 ± 0.65 years because of psychosocial difficulties in coping with the relatively early puberty: one from the subgroup with no BA advancement (6%), 6 from the subgroup with mild advancement (17%), and 5 from the subgroup with moderate advancement (17%). The clinical characteristics of these girls were indistinguishable from those of the remaining 73 girls for degree of pubarche and DHEA-S levels at diagnosis of PA and CA, BA SDS, Ht SDS, and BMI SDS at diagnosis and at onset of puberty. At initiation of treatment (CA, 9.5 ± 0.76 years), the girls' gonadarchal stage was 2 to 3 (Tanner), and their Ht SDS was 0.95 ± 0.83. After cessation of therapy, at CA of 10.8 ± 0.74 years, spontaneous resumption of puberty was demonstrated in all girls, with menarche occurring at CA 12.2 ± 0.57 years. Because of the GnRHa therapy, these 12 girls were excluded from the analysis of pubertal course, age of menarche, and adult height.

In the remaining 73 girls, duration of puberty and total pubertal growth were within the reference range and were similar in the 3 subgroups. Their age at menarche was significantly earlier than that of the control group (12.4 ± 1.2 years versus 13.2 ± 1.3 years, $P < .02$).

Sequential Auxological Characteristics of the 73 Girls with PA Stratified by the Degree of BA Advancement

Ht SDS was significantly higher at diagnosis in the girls with PA with more advanced BA ($P = .002$) and remained so, although to a lesser extent, at onset of pubertal development ($P = .01$; Table and Figure 1). Throughout follow-up, Ht SDS significantly decreased in the whole study cohort ($P < .001$), with no statistical interaction in the 3 subgroups (Figure 1, A).

BMI SDS did not differ significantly in the 3 subgroups at diagnosis, at onset of puberty, or at early adulthood. Longitudinal analysis yielded a significant decrease in BMI SDS for the entire cohort from diagnosis to early adulthood ($P < .001$), with no statistical interaction in the 3 subgroups (Figure 1, B).

Longitudinal analysis of the degree of bone maturation from diagnosis to onset of puberty (expressed as BA SDS) showed a significant change in the 3 subgroups ($P < .001$), with a statistically significant group interaction ($P = .03$). Whereas in the moderately advanced BA subgroup, BA was more advanced already at diagnosis and remained so at onset

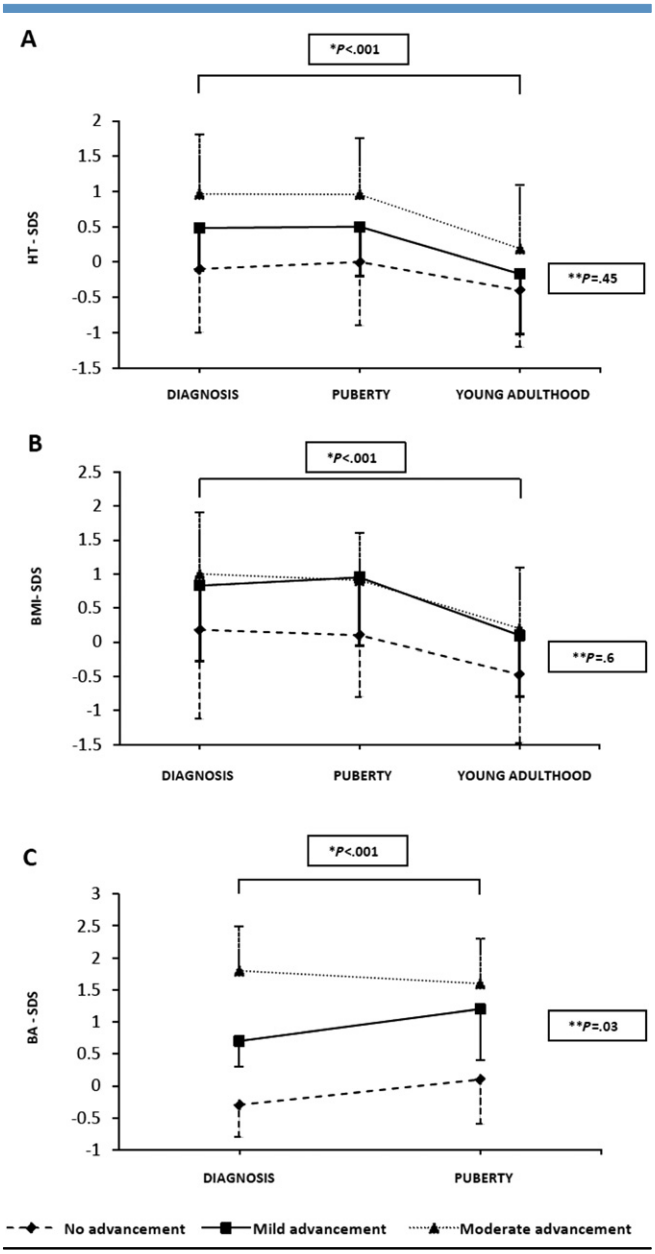

Figure 1. Sequential auxological characteristics of girls with PA stratified by the degree of BA advancement at diagnosis, at onset of puberty, and at young adulthood. **A,** Ht SDS. **B,** BMI SDS. **C,** BA SDS. *Time interaction. **Between-group interaction.

of puberty, in the other two subgroups BA SDS significantly increased toward the onset of puberty (Figure 1, C).

Achieved and Predicted Adult Height of the 73 Girls with PA

Adult height of the girls with PA was similar and did not differ significantly from their respective MPHt (163.2 ± 5.8 cm versus 161.7 ± 5.8 cm, respectively; Figure 2). Adult height prediction at diagnosis as compared with achieved adult height revealed a statistically significant group interaction in the 3 subgroups ($P < .001$). In the moderately advanced BA subgroup, adult height prediction significantly underestimated achieved adult height ($P < .001$); in the mildly advanced BA subgroup, PAHt was relatively accurate; in the subgroup with no BA advancement, PAHt overestimated achieved height ($P = .04$).

Discussion

We found that the natural history of girls with more extensive adrenarche, more advanced BA, and higher DHEA-S levels at referral was associated with a taller stature, persistent advanced BA, and poor height prognosis during childhood. However, similar to the girls with the less pronounced presentation, they displayed a normal pubertal onset with relatively early menarche and attained an uncompromised adult height within their MPHt range.

At diagnosis, the clinical manifestations of the studied girls ranged from minimal sexual hair and no BA advancement to extensive distribution of pubic hair, axillary hair, or both and a difference between BA and CA >1 year. The underlying cause accounting for the wide range of clinical-laboratory features, particularly in girls with the more pronounced adrenarche, is not well established. Earlier studies reported associations between extensive pubarche at presentation and low birth weight,[6,8] obesity,[5,18,19] and "exaggerated adrenarche."[20] In our cohort, all the girls were born AGA, and none were obese at diagnosis or throughout follow-up. Moreover, basal levels of Δ4A, testosterone, and post- corticotropin stimulation-17OHP were within the pre-pubertal reference range irrespective of the degree of adrenarche at presentation, in contrast to girls with "exaggerated adrenarche," who had relatively elevated levels of these hormones.

The extent of hormonal dysregulation underlying PA in girls in our cohort, as evidenced by DHEA-S levels at presentation, affected their growth and bone maturation rate. In accordance with earlier studies,[1-4] the growth pattern of all girls was

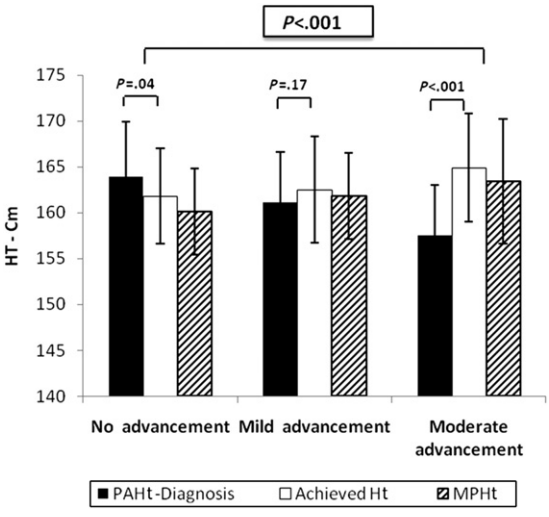

Figure 2. Comparison between achieved adult height, PAHt at diagnosis (calculated according to Bailey and Pinneau), and mid-parental height in AGA girls with PA.

characterized by enhanced growth during childhood that waned in puberty. Yet girls with the pronounced adrenarche and the higher DHEA-S levels were significantly taller and displayed a more advanced BA, particularly through childhood. This finding may reflect the earlier onset of the underlying endocrinopathy in these girls, as previously suggested by Utriainen et al.[21] DHEA-S is considered to be a weak androgen; however, it is plausible that in early childhood the increased DHEA-S levels were able to accelerate bone elongation and maturation, either directly or through peripheral conversion to sex hormones. The taller stature also could stem from higher insulin-like growth factor (IGF)-1 levels: earlier studies found that in girls with PA, IGF-1 levels already were high in early childhood.[21,22] Thus, it may be speculated that IGF-1 levels were relatively higher in those of our girls showing more extensive adrenarche. Unfortunately, this assumption could not be evaluated in the present study setting since IGF-1 levels were not routinely measured.

The evolution of bone maturation in our girls also was distinct. Although the marked BA advancement exhibited by the girls with the more extensive adrenarche at presentation was progressively attenuated in late childhood and at initiation of puberty, the BA of girls with the less extensive adrenarche continued to accelerate throughout childhood. The pathophysiology underlying these patterns is not well established.

In contrast to earlier studies showing that in girls with PA predicted adult height at diagnosis correlated with the achieved adult height,[3,4] in most of our cohort adult height prediction was inaccurate. The achieved adult height proved to have been underestimated when BA at presentation was one or more years ahead of CA, and overestimated when BA corresponded to CA. The classic methods of Bayley and Pinneau for predicting adult height, with the tables of "average," "accelerated," or "retarded" children as appropriate, are mainly based on growth data from children with no underlying endocrinopathy.[23] Applying the same means for determining adult height in children with an unusual evolution of skeletal maturation, such as that displayed by this cohort, may yield inaccurate results. Our entire cohort attained a similar uncompromised adult height within their MPHt range despite the variations in the degree of adrenarche at presentation and regardless of the heterogeneity in growth pattern and skeletal maturation throughout follow-up. This observation is consistent with earlier studies[2,3,4] and emphasizes the transient effect of PA on growth and its negligible effect on adult height.

Pubertal development and growth in our cohort was similar across the entire cohort. Moreover, onset of puberty, duration of puberty, and total pubertal growth were within the reference range. However, menarche occurred at a significantly younger age than in the control group and in the general Israeli population.[24] Early onset of puberty and faster transit through puberty has been reported in girls with PA born SGA[6,12,25] and in girls who were overweight in childhood.[19] In these populations, hyperinsulinemia, increased leptin levels, or both, characteristic features of both SGA girls and overweight girls, were considered to underlie their pubertal course.[26,27] Our cohort was neither low birth weight nor obese. Thus the relatively early menarche might be associated with the increased androgen levels observed during childhood as suggested by Remer et al.[28] Alternatively, the relatively early menarche may be attributable to an as yet undefined continuous endocrine dysfunction underlying PA in girls born AGA.

Our study has several limitations. Omission of the 12 girls who received GnRHa from the analysis of pubertal course, menarche, and adult height could have altered the statistical conclusions. However, it appeared that these girls did not differ from the entire cohort either at presentation or at onset of puberty. Furthermore, the decision to initiate GnRHa therapy stemmed mainly from psychological concerns and not from differences in growth pattern and pubertal onset and course. In addition, because this study was retrospective, there are no available data on the evolution of hormonal levels; a sustained elevation or further rise in blood concentration of adrenal androgens, insulin, IGF-1, or leptin during the follow-up period could have affected the clinical course. Moreover, genetic analysis was not yet a realistic tool in the years covered by the study. Recent reports indicate possible associations between PA and variations in genes involved in steroid synthesis,[29] androgen action,[30] and insulin and IGF functions.[31] It is plausible that assessment of genes involved in steroid synthesis and androgen action might have provided a better understanding of the phenotypic variability in our study subjects.

Our longitudinal follow-up study of AGA girls with PA stratified according to the degree of BA advancement may serve as a valuable tool in clinical practice. Our findings indicate that an even more extensive PA and a BA advancement >1 year at presentation in AGA girls in whom the results of a comprehensive initial work-up were negative were not associated with increased risk for early and rapid progression of puberty and reduced adult height, as previously suspected.

As with AGA girls showing a less extensive adrenarche, reassurance of the patients and their families and limited follow-up are the key to the treatment of this population. Height prediction should be used cautiously in girls with PA, irrespective of their degree of BA advancement, because it was found to be inaccurate in the girls with the more advanced BA and in girls with no BA advancement. ■

Submitted for publication Apr 26, 2011; last revision received Jun 24, 2011; accepted Aug 2, 2011.

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