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Early Puberty-Menarche After Precocious Pubarche: Relation to Prenatal Growth

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ABSTRACT

OBJECTIVE. Girls with precocious pubarche (PP; pubic hair at <8 years of age) as a result of an early or amplified adrenarche (high dehydroepiandrosterone-sulfate [DHEAS]) tend to be hyperinsulinemic, in particular when born with low birth weight (LBW). The objective of this study was to assess the interrelationship among prenatal growth, PP, the timing of puberty-menarche, and adult stature.

METHODS. We studied 187 PP girls longitudinally: (1) at birth, (2) in prepuberty, (3) at onset of puberty, (4) at menarche, and (5) on reaching adult stature. This PP cohort was divided into subgroups of higher birth weight (>0 SD), intermediate birth weight (0 to -2 SD), and lower birth weight (less than -2 SD).

RESULTS. At the time of PP diagnosis, age, bone age, and BMI were similar across birth weight subgroups; circulating sex hormone-binding globulin and body height were reduced in PP girls with lower birth weight, and these remained so throughout pubertal development. Onset of puberty occurred earlier in PP girls with lower birth weight; so did menarche. Adult height differed by an average of 6.5 cm (~1 SD) between the upper and lower birth weight subgroups; this difference was essentially achieved before puberty and even before PP. Menarche before age 12.0 years was twofold more prevalent in PP girls than in control subjects. Among PP girls, age at menarche was advanced by 8 to 10 months in lower versus higher birth weight girls. Menarche before age 12.0 years was threefold more prevalent among LBW-PP girls than in control subjects (~75% vs ~25%).

CONCLUSIONS. The link between prenatal growth restraint and early menarche is herewith extended to PP girls. In particular LBW-PP girls may become a target group for interventions directed toward normalization of pubertal onset and progression.

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Key Words

precocious pubarche, adrenarche, birth weight, growth, puberty, height

Abbreviations

PP—precocious pubarche
DHEAS—dehydroepiandrosterone-sulfate
LBW—low birth weight
SHBG—sex hormone-binding globulin
B2—Tanner stage 2 for breast development
SDS—SD score

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GIRLS WITH PRECOCIOUS pubarche (PP; pubic hair at <8 years of age) as a result of an early or amplified adrenarche (high circulating dehydroepiandrosterone-sulfate [DHEAS])¹ tend to be hyperinsulinemic, in particular when born with low birth weight (LBW); this hyperinsulinemia is reflected, for example, by low insulin-like growth factor binding protein-1 and sex hormone-binding globulin (SHBG) levels and also by a central fat excess.¹⁻³

The majority of LBW girls demonstrate vigorous catch-up growth in infancy and, by the age of 1 year, become insulin resistant⁴; by 2 years of age, they have normalized height and weight,⁵ and by 3 years of age, they start to have an adipose body composition.⁶ By 8 years of age, girls with the combination of a birth weight in the lower tertile and an actual weight in the upper tertile develop an amplified adrenarche⁷ that may be accompanied by PP (depending on background genotype) and that can be followed by hyperinsulinemic hyperandrogenism, so-called polycystic ovary syndrome.^{1,8-11}

Longitudinal follow-up of girls with PP has shown that, on average, these girls present an early-normal onset and progression of puberty and an adult stature within target height range.¹² However, the interrelation-

ships among prenatal growth, PP, the timing of puberty-menarche, and adult stature remain to be defined.

Methods

Study Population

We studied the longitudinal data from 187 Catalan (Northern Spanish) girls who had PP and were followed in Barcelona up to adult height. On each girl, information was available at 5 consecutive stages: (1) at birth (medical records); (2) in prepuberty (within 6 months after PP diagnosis); (3) at onset of puberty (Tanner stage 2 for breast development [B2]¹³); (4) at menarche (within 6 months of first menstrual period); and (5) on reaching adult stature.

The study population consisted only of girls in whom PP was ascribed to amplified adrenarche, as suggested by high serum androstenedione and/or DHEAS levels¹; mean delay between pubic hair appearance and diagnostic evaluation was estimated to be in the 6- to 12-month range. None of the girls presented evidence for late-onset adrenal hyperplasia,^{14,15} thyroid dysfunction, or diabetes or was receiving medications that are known to affect adrenal or gonadal function or carbohydrate or lipid metabolism.

TABLE 1 Sequential Characteristics, From Birth Up to Adult Height, in the Total Study Population of Girls With PP, Who Were Subgrouped According to Birth Weight for Gestational Age

	Total (n = 187)	Birth Weight >0 SD (n = 43)	Birth Weight From 0 to -2 SD (n = 94)	Birth Weight less than -2 SD (n = 50)
Birth				
Weight, kg	2.8 (0.04)	3.5 (0.4)	2.8 (0.4)	2.2 (0.05) ^a
Weight for gestational age, SD	-1.1 (0.1)	0.5 (0.1)	-1.1 (0.1)	-2.6 (0.1) ^a
Diagnosis of PP				
Age, y	6.9 (0.1)	7.0 (0.1)	6.9 (0.1)	6.9 (0.1)
Bone age, y	8.0 (0.1)	8.0 (0.1)	8.1 (0.1)	8.1 (0.1)
Height, cm	126.2 (0.6)	128.8 (1.1)	126.2 (0.8)	123.9 (1.1) ^b
BMI, SD	0.7 (0.1)	0.8 (0.2)	0.8 (0.2)	0.5 (0.2)
SHBG, nmol/L	66 (2)	74 (5)	65 (3)	59 (3) ^b
Onset of puberty				
Age, y	9.6 (0.1)	9.9 (0.1)	9.5 (0.1)	9.4 (0.1) ^b
Bone age, y	10.9 (0.04)	11.0 (0.1)	10.9 (0.1)	10.8 (0.1) ^c
Height, cm	139.8 (0.5)	143.2 (0.8)	139.7 (0.6)	137.0 (0.8) ^a
BMI, SD	0.7 (0.1)	0.7 (0.2)	0.7 (0.1)	0.6 (0.2)
SHBG, nmol/L	45 (1)	53 (3)	45 (2)	40 (2) ^a
Menarche				
Age, y	11.9 (0.1)	12.3 (0.1)	11.9 (0.1)	11.5 (0.1) ^a
Height, cm	155.7 (0.4)	159.0 (0.7)	155.6 (0.6)	153.1 (0.8) ^a
BMI, SD	0.5 (0.1)	0.3 (0.2)	0.6 (0.1)	0.4 (0.2)
SHBG, nmol/L	40 (1)	49 (4)	38 (2)	37 (2) ^b
Adult height				
Pubertal height gain, cm	20.9 (0.3)	21.1 (0.8)	20.9 (0.4)	20.9 (0.6)
Adult height, cm	160.7 (0.4)	164.3 (0.7)	160.6 (0.6)	157.8 (0.8) ^a
Midparental height, cm	158.5 (0.3)	159.4 (0.6)	158.8 (0.5)	157.1 (0.6) ^b
Adult height minus midparental height, cm	2.2 (0.3)	4.9 (0.5)	1.7 (0.4)	0.7 (0.6) ^a

Values are mean (SEM). Mean reference values for SHBG are 93 nmol/L in prepuberty and 65 nmol/L in early and late puberty.¹ SHBG indicates sex hormone-binding globulin.

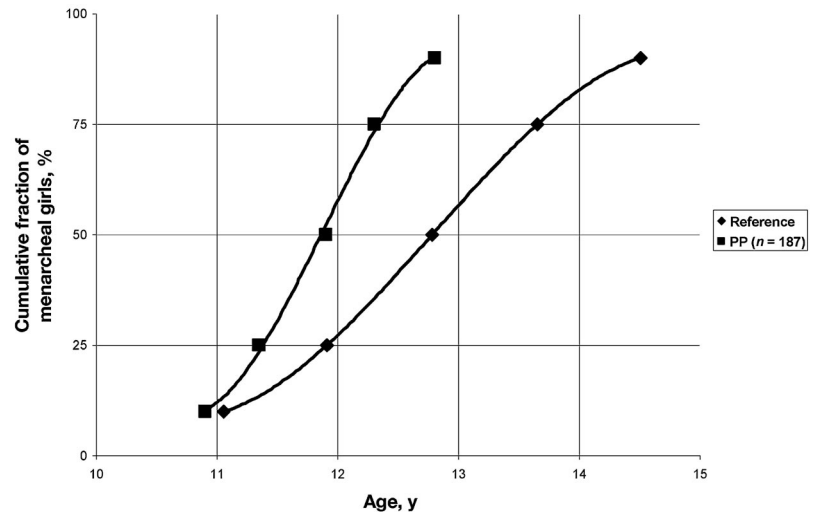
^a $P \leq .001$ versus birth weight >0 SD, with intermediate results for the intermediate birth weight group.

^b $P \leq .01$ versus birth weight >0 SD, with intermediate results for the intermediate birth weight group.

^c $P \leq .05$ versus birth weight >0 SD, with intermediate results for the intermediate birth weight group.

FIGURE 1

Distribution of age at menarche in PP girls and in a general population from the same region. At 11 years of age, the fraction of premenarcheal girls is ~90% in both the PP girls and the general population. By the age of 12.8 years, however, the fraction of premenarcheal girls is fivefold larger in the general population than among PP girls. ◆, reference; ■, PP (*n* = 187).



Auxology

Height was measured with a Harpenden stadiometer and transformed into an SD score (SDS) according to Tanner references,¹⁶ which were appropriate for Catalan girls over the time span of follow-up.¹⁷ Adult height was considered to be reached when postmenarchal growth velocity had decreased to <0.5 cm/year and/or when bone age was ≥ 15 years. Target height was defined as midparental height, adjusted for female gender. BMI was calculated as a ratio of weight (in kilograms) to height squared (in meters) and was transformed into SDSs³; bone age was assessed by a single observer, according to the method of Greulich and Pyle.¹⁸

Birth weight data were transformed into SDSs for gestational age, as described.¹ To assess the effect of birth weight on menarche and on auxologic and biochemical variables, the PP cohort was divided into subgroups of higher birth weight (>0 SD), intermediate birth weight (0 to -2 SD), and lower birth weight (less than -2 SD); at term birth, these SD values correspond to birth weights of approximately >3.4, 3.4 to 2.5, and <2.5 kg.¹

Hormonal Assessment and Assays, Statistics, and Ethics

In all girls, serum SHBG levels were assessed by immunochemiluminescence (Immulite 2000; Diagnostic Products, Los Angeles, CA); 17-hydroxyprogesterone was measured by a commercial radioimmunoassay, as described.³ Samples were stored at -20°C until assay.

This study was approved by the institutional review board of Barcelona Hospital. Two-sided *t* tests (paired or unpaired, as appropriate) were used for comparisons; per variable, only 1 comparison was performed; significance level was set at $P < .05$. Selected results from part of this study population were previously reported within other contexts.^{1,3,8}

RESULTS

Table 1 summarizes the sequential characteristics of PP girls, as subgrouped by birth weight for gestational age.

At birth, the mean birth weight of PP girls centered around -1 SD, as expected.¹ At the time of PP diagnosis, age, bone age, and BMI were similar across birth weight subgroups; circulating SHBG and body height were lower in PP girls with lower birth weight, and these remained so throughout pubertal development. Onset of puberty (B2) occurred earlier in PP girls with lower birth weight and so did menarche. Adult height differed by an average of 6.5 cm (~1 SD) between the upper and lower birth weight subgroups. This difference was essentially achieved before puberty and even before PP; pubertal height gain was strikingly similar in all birth weight groups.

Figure 1 shows the distribution of age at menarche in PP girls. A comparison with the general distribution of menarcheal age in Barcelona¹⁹ discloses that the prevalence of menarche before age 12 or 13 years is strikingly higher among PP girls. At the age of 11 years, ~90% of girls in both the PP and the general population are still premenarcheal. Before the age of 12.0 years, however, the prevalence of menarche doubles in PP girls, as compared with the general population. At the age of 12.8 years, the fraction of premenarcheal girls is fivefold larger in the general population than among PP girls.

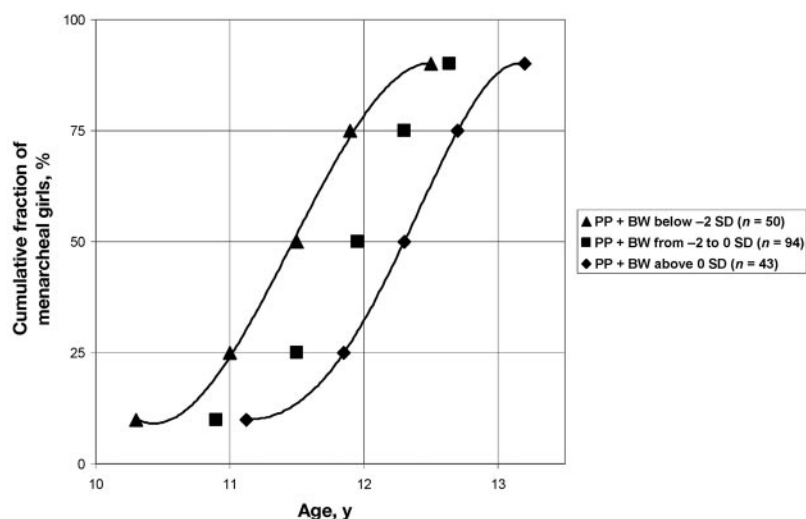
Figure 2 displays the distributions of menarcheal age in birth weight subgroups of PP girls. Time at menarche was advanced ($P < .001$) by 8 to 10 months in lower birth weight versus higher birth weight girls, whereas intermediate birth weight girls showed an intermediate pattern. Menarche before age 12.0 years was threefold more prevalent among LBW-PP girls than in the general population (~75% vs ~25%).

DISCUSSION

When the onset of puberty (B2) occurs in the normal age range, an earlier start of puberty tends to be compensated by a longer pubertal course to menarche: the time from B2 to menarche spans on average 3.2 years

FIGURE 2

Distributions of menarcheal age in birth weight subgroups of PP girls. Time at menarche was advanced ($P < .001$) in lower versus upper birth weight girls; intermediate birth weight girls showed an intermediate pattern. ▲, PP + birth weight less than -2 SD ($n = 50$); ■, PP + birth weight from -2 SD to 0 SD ($n = 94$); ◆, PP + birth weight >0 SD ($n = 43$).



when B2 occurs at 8 years of age, whereas it spans on average 0.7 years when B2 occurs at 13 years of age.^{20,21} This compensation explains why the age of menarche varies less than the age of pubertal onset.^{20,21} For unknown reasons, such compensation seems to be less operational in LBW girls: their onset of puberty is advanced by ~6 months, and menarche is also advanced by ~6 months, or by even more.^{22,23} Among girls who start puberty at 8 years of age, menarche occurs 1 year earlier in LBW than in non-LBW girls, and such rapid pubertal progression may contribute to shortening adult stature.²⁴ However, the main cause of the relatively short adult stature of LBW-PP girls seems to be their prenatal growth restraint, because most of their height loss occurred before puberty and even before PP.

In population studies, early menarche has been associated with fat excess and with higher fasting levels of insulin.^{25,26} Given that both LBW and PP girls are characterized by hyperinsulinemia,²⁷⁻²⁹ the present findings could be interpreted as suggestive of a stimulatory role for hyperinsulinemia (and/or its correlates) in the tempo of pubertal progression. From prepuberty to postmenarche, LBW-PP girls displayed low levels of circulating SHBG, which is a marker of hyperinsulinemic insulin resistance in nondiabetic girls.³⁰ In LBW-PP girls, not only the low levels of SHBG but also the hyperleptinemia may participate in the acceleration of both the onset and progression of puberty.^{30,31}

The link between prenatal growth restraint and early menarche, as previously established for girls with early-normal onset of puberty,²⁴ is herewith extended to girls with PP. The described acceleration of pubertal onset and progression remains to be confirmed in ethnic or other populations with a relatively high prevalence of LBW, early pubarche, overweight, and, maybe, high androgen sensitivity.^{9,25,26,32,33} If the present findings are confirmed, then LBW-PP girls may become a target

group for interventions that are directed not only toward prevention of hyperinsulinemic hyperandrogenism^{10,34} but also toward normalization of pubertal onset and progression.

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