Early Puberty: Rapid Progression and Reduced Final Height in Girls With Low Birth Weight

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ABSTRACT. Objective. To assess whether, in girls with early onset of puberty, low birth weight is a risk factor for rapid progression to menarche and for short adult stature.

Design. Longitudinal clinical assessment of 54 Catalan (Northern Spanish) girls followed from early onset of puberty (onset of breast development between 8.0 and 9.0 years of age) to final height. The timing of menarche and the final height were analyzed a posteriori according to birth weight, the cutoff level between normal and low birth weight subgroups being −1.5 standard deviation (SD: ~2.7 kg at term birth).

Results. Normal and low birth weight girls had similar target heights and characteristics at diagnosis of early puberty. However, menarche occurred on average 1.6 years earlier in low versus normal birth weight girls (11.3 ± .3 years vs 12.9 ± .2 years), and final height was >5 cm shorter in low birth weight girls (parental adjusted height SD: −.6 ± .2 cm vs .3 ± .2 cm).

Conclusion. The timing of menarche and the level of final height in Catalan girls with early onset of puberty was found to depend on prenatal growth. Girls with normal birth weight tend to progress slowly through puberty with a normal timing of menarche and normal final height. In contrast, girls with low birth weight tend to progress relatively rapidly to an early menarche and to a reduced final height. If these findings are confirmed in other ethnic and/or larger groups, then a subgroup has been identified that will most likely benefit from any therapeutic intervention aiming at a delay of pubertal development and/or an increase of final height.

METHODS

The study population consisted of all 54 Catalan (Northern Spanish) girls with early/normal onset of breast development, who had been followed up to final height in the Pediatric Endocrine Unit of Barcelona (Barcelona, Spain) over the past decade (1986–1997). At that time, it was estimated that <4% to 6% of Catalan girls experienced onset of puberty before 9 years of age.3

The diagnosis of early/normal puberty was made on referral and was based on: 1) onset of breast development (with or without pubarche) between 8.0 and 9.0 years of age and within the preceding 3 to 6 months;2) 2) uterine corpus length >40 mm on ultrasound examination; and 3) peak plasma luteinizing hormone >8 UI/L in response to gonadotropin-releasing hormone.10

Height was measured with a Harpenden (Wima Technik AG, Rapperswil, Switzerland) stadiometer and transformed into standard deviation (SD) scores according to Tanner references,13 which were appropriate for Catalan children over the time span of follow-up.12 Final height was considered to be reached when postmenarcheal growth velocity had decreased to <.5 cm/year and/or when bone age was ≥15.0 years.

Birth weight and gestational age data were obtained from hospital records and transformed into SD scores for gestational age, as described13; the population was divided into normal and low birth weight subgroups according to a cutoff level of −1.5 SD (~2.7 kg at term birth), a level of prenatal growth restriction that is associated with subsequent ovarian hyperandrogenism and hyperinsulinism in girls with a history of precocious pubarche.13

Target height was defined as midparental height adjusted for female gender. Bone age was assessed by a single observer, according to the method of Greulich and Pyle.14

Data are expressed as mean ± standard error of the mean; t tests were used for comparisons with P values <.05 considered statistically significant.
RESULTS

Table 1 summarizes the clinical variables observed in the study population at birth, at time of diagnosis, at menarche, and at final height.

Overall, the cohort was found to have a relatively low birth weight SD score of $-6 \pm 1$ (mean weight: $\sim3.1$ kg at term birth) and also a low target height SD score of $-9 \pm 1$ (mean height: 156.6 $\pm$ .7 cm). In line with previous reports, the average bone age was advanced at the time of diagnosis, mean age at menarche was normal, and the final height was at target level.

Subdividing the cohort according to birth weight revealed that the target heights of the 2 subgroups were comparable, as were their characteristics at diagnosis of early puberty. Thereafter, however, major differences between the subgroups were disclosed: girls with a lower birth weight (mean weight: $\sim2.5$ kg at term birth) experienced menarche, on average, 1.6 years earlier, and their mean final height was reduced by $>5$ cm.

DISCUSSION

Whether girls with early onset of puberty have a normal timing of menarche and reach target height was found to depend on their prenatal growth status, as assessed by birth weight for gestational age. Hence, our findings in these girls extent the principle applicable to girls with pubertal onset after 9 years of age, namely that an earlier onset of breast development is followed by a longer interval to menarche.

In contrast, if prenatal growth was reduced, then girls with onset of puberty at 8 years of age seem to progress, on average, slowly through puberty and to experience a normal timing of menarche. Hence, these girls seem to be incompletely protected by the aforementioned mechanism that compensates an early onset of puberty by a slower progression to menarche and by a longer duration of the pubertal growth spurt. The sequence of low birth weight, early and rapidly progressive puberty, and short adult stature has recently been noted in girls with uniparental disomy of chromosome 14. It remains to be verified to which extent the failure of the compensatory mechanism in these girls is orchestrated by changes in hypothalamo-pituitary function and/or by altered target organ responsiveness to hormonal stimulation by, for example, follicle-stimulating hormone, insulin, and growth hormone. Regardless of the mechanisms that will prove to be involved, if the described acceleration of menarche and the reduction of final height are perceived as clinically relevant and are confirmed in other ethnic and/or larger groups, then girls with the combination of low birth weight and early onset of puberty may be the subgroup that is most likely to benefit from any therapeutic intervention aimed at a delay of pubertal development and/or an increase of final height. Henceforth, these observations may also be relevant when interpreting the effect of gonadotropin-releasing hormone-analogue treatment on the final height of girls with early onset of puberty, or when judging the effect of GH treatment on the pubertal progression of girls with short stature after prenatal growth restriction.

TABLE 1.

Characteristics of the Study Population of Girls With Early Puberty

<table>
<thead>
<tr>
<th></th>
<th>Total $n = 54$</th>
<th>Birth Weight SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\geq-1.5$ SD</td>
<td>$&lt;-1.5$ SD</td>
</tr>
<tr>
<td>$n = 42$</td>
<td>$n = 12$</td>
<td></td>
</tr>
<tr>
<td>Birth weight SDS</td>
<td>$-6 \pm 2^*$</td>
<td>$-1 \pm 1$</td>
</tr>
<tr>
<td>$-2.2 \pm 2$</td>
<td>$-9 \pm 1^*$</td>
<td>$-9 \pm 1$</td>
</tr>
<tr>
<td>$-9 \pm 3$</td>
<td>$-9 \pm 3$</td>
<td>$-9 \pm 3$</td>
</tr>
<tr>
<td>Target height SDS</td>
<td>$-0.3$</td>
<td>$-0.3$</td>
</tr>
<tr>
<td>Onset of puberty (B2)</td>
<td>$8.6 \pm 1$</td>
<td>$8.6 \pm 1$</td>
</tr>
<tr>
<td>Chronological age (y)</td>
<td>$9.8 \pm 1$</td>
<td>$9.7 \pm 2$</td>
</tr>
<tr>
<td>$10.0 \pm 2$</td>
<td>$10.0 \pm 2$</td>
<td>$10.0 \pm 2$</td>
</tr>
<tr>
<td>Bone age (y)</td>
<td>$131.9 \pm 12$</td>
<td>$132.8 \pm 14$</td>
</tr>
<tr>
<td>$128.6 \pm 2.7$</td>
<td>$128.6 \pm 2.7$</td>
<td></td>
</tr>
<tr>
<td>$128.6 \pm 2.7$</td>
<td>$128.6 \pm 2.7$</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>$182.2 \pm 3$</td>
<td>$181.1 \pm 4$</td>
</tr>
<tr>
<td>$187.7 \pm 7$</td>
<td>$187.7 \pm 7$</td>
<td></td>
</tr>
<tr>
<td>$187.7 \pm 7$</td>
<td>$187.7 \pm 7$</td>
<td></td>
</tr>
<tr>
<td>Menarche (y)</td>
<td>$12.2 \pm 2$</td>
<td>$12.2 \pm 2$</td>
</tr>
<tr>
<td>$11.3 \pm 3^#$</td>
<td>$11.3 \pm 3^#$</td>
<td></td>
</tr>
<tr>
<td>$11.3 \pm 3^#$</td>
<td>$11.3 \pm 3^#$</td>
<td></td>
</tr>
<tr>
<td>Final height</td>
<td>$157.2 \pm 9$</td>
<td>$158.3 \pm 10$</td>
</tr>
<tr>
<td>$153.0 \pm 1.5$</td>
<td>$153.0 \pm 1.5$</td>
<td></td>
</tr>
<tr>
<td>$153.0 \pm 1.5$</td>
<td>$153.0 \pm 1.5$</td>
<td></td>
</tr>
<tr>
<td>Height SDS</td>
<td>$-0.1 \pm 1$</td>
<td>$-0.3 \pm 2$</td>
</tr>
<tr>
<td>Adjusted height</td>
<td>$-0.6 \pm 2^*$</td>
<td>$-0.6 \pm 2^*$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ standard error of the mean. B2 indicates Tanner breast stage II; BMI, body mass index; SDS, standard deviation score.

$^*$ P < .001 versus normal distribution (1-sample t test).

$^*$ P $= .01$ versus girls with birth weight $\geq-1.5$ SD.

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