

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

Lourdes Ibáñez, MD, PhD\*; Angela Ferrer, MD, PhD\*; Maria Victoria Marcos, MD‡; Francisco Rodriguez Hierro, MD, PhD\*; and Francis de Zegher, MD, PhD§

**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;  $\sim 2.7$  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 ( $11.3 \pm .3$  years vs  $12.9 \pm .2$  years), and final height was  $>5$  cm shorter in low birth weight girls (parental adjusted height SD:  $-.6 \pm .2$  cm vs  $.3 \pm .2$  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. *Pediatrics* 2000;106(5). URL: <http://www.pediatrics.org/cgi/content/full/106/5/e72>; *early puberty, final height, low birth weight.*

ABBREVIATION. SD, standard deviation.

Nowadays, puberty starts in girls at a younger age than in previous generations; for example, in the United States, onset of breast development occurs at a mean age of 10.0 years.<sup>1,2</sup> If pubertal development starts before the age of 6 to 7 years, there is consensus that an evaluation is war-

ranted, in part, because of the risk for early menarche and short final height. These risks seem to be no longer relevant when the onset of puberty occurs after the age of 9 years, because an earlier onset after that age is usually compensated by a slower rate of pubertal progression.<sup>3</sup> Current debate thus focuses on early/normal puberty starting at  $\sim 7$  to 8 years of age, a specific question being whether there is a subgroup that may, nevertheless, be at risk for early menarche and reduced final height. On a quantitative basis, the latter question is primarily relevant for girls starting puberty at 8 years of age and, in particular, for those having rather short parents.

We hypothesized that, among the girls with early/normal onset of puberty, those with a low birth weight may be at risk for rapid progression and for reduced final height. This hypothesis was based on the previous identification of low birth weight in girls as a risk factor for subsequent short stature, exaggerated adrenarche, and ovarian dysfunction.<sup>4-6</sup> We have now tested this hypothesis in a cohort of girls with onset of puberty at 8 years of age.

## 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.<sup>3</sup>

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<sup>7,8</sup>; 2) uterine corpus length  $>40$  mm on ultrasound examination<sup>9</sup>; and 3) peak plasma luteinizing hormone  $>8$  UI/L in response to gonadotropin-releasing hormone.<sup>10</sup>

Height was measured with a Harpenden (Wima Technik AG, Rapperswil, Switzerland) stadiometer and transformed into standard deviation (SD) scores according to Tanner references,<sup>11</sup> which were appropriate for Catalan children over the time span of follow-up.<sup>12</sup> Final height was considered to be reached when postmenarcheal growth velocity had decreased to  $<.5$  cm/year and/or when bone age was  $\geq 15.0$  years.

Birth weight and gestational age data were obtained from hospital records and transformed into SD scores for gestational age, as described<sup>13</sup>; the population was divided into normal and low birth weight subgroups according to a cutoff level of  $-1.5$  SD ( $\sim 2.7$  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.<sup>13</sup>

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.<sup>14</sup>

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

From the \*Endocrinology Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain; ‡Endocrinology Unit, Consorci Hospitalari de Terrassa, Terrassa, Spain; and the §Department of Paediatrics, University of Leuven, Leuven, Belgium.

Received for publication Apr 21, 2000; accepted Jun 27, 2000.

Reprint request to (L.I.) Endocrinology Unit, Hospital Sant Joan de Déu, University of Barcelona, Passeig de Sant Joan de Déu 2, 08950, Esplugues, Barcelona, Spain. E-mail: libanez@hsjdbcn.org

PEDIATRICS (ISSN 0031 4005). Copyright © 2000 by the American Academy of Pediatrics.

## 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  $-0.6 \pm 0.1$  (mean weight:  $\sim 3.1$  kg at term birth) and also a low target height SD score of  $-0.9 \pm 0.1$  (mean height:  $156.6 \pm 0.7$  cm). In line with previous reports, the average bone age was advanced at the time of diagnosis, mean age at menarche was normal,<sup>3,12</sup> 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:  $\sim 2.5$  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.

If prenatal growth was not reduced, then girls with an 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, our findings in these girls extend 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.<sup>3</sup>

In contrast, if prenatal growth was reduced, then girls with onset of puberty at 8 years of age were found to experience menarche early and to have a reduced final height. Thus, 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.<sup>15</sup> 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.<sup>5,16–20</sup> 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-analog 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.

## ACKNOWLEDGMENTS

This work was supported by a scholarship from the European Society for Paediatric Endocrinology.

F.d.Z. is a clinical research investigator of the Fund for Scientific Research (Flanders, Belgium).

We thank Karin Vanweser for editorial assistance.

## REFERENCES

- Herman-Giddens ME, Slora EJ, Wasserman RC. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network. *Pediatrics*. 1997;99:505–512
- Kaplowitz PB, Oberfield SE, and the Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. *Pediatrics*. 1999;104:936–941
- Marti-Henneberg C, Vizmanos B. The duration of puberty in girls is related to the timing of its onset. *J Pediatr*. 1997;131:618–621
- de Zegher F, Francois I, van Helvoirt M, van den Berghe G. Small as a fetus and short as a child: from endogenous to exogenous growth hormone. *J Clin Endocrinol Metab*. 1997;82:2021–2026
- Ibáñez L, Potau N, Marcos MV, de Zegher F. Exaggerated adrenarche and hyperinsulinism in adolescent girls born small for gestational age. *J Clin Endocrinol Metab*. 1999;84:4739–4741
- Ibáñez L, de Zegher F, Potau N. Anovulation after precocious pubarche: early markers and time course in adolescence. *J Clin Endocrinol Metab*. 1999;84:2691–2695
- Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. *Arch Dis Child*. 1969;44:291–303
- Bouvattier C, Coste J, Rodrigue D, et al. Lack of effects of GnRH agonists on final height in girls with advanced puberty: a randomized long-term pilot study. *J Clin Endocrinol Metab*. 1999;84:3575–3578
- Griffin IJ, Cole TJ, Duncan KA, Hollman AS, Donaldson MDC. Pelvic ultrasound measurements in normal girls. *Acta Paediatr*. 1995;84:536–543
- Ibáñez L, Potau N, Zampolli M, et al. Use of leuprolide acetate response patterns in the early diagnosis of pubertal disorders: comparison with the gonadotropin-releasing hormone test. *J Clin Endocrinol Metab*. 1994;78:30–35
- Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. *Arch Dis Child*. 1986;41:613–635

**TABLE 1.** Characteristics of the Study Population of Girls With Early Puberty

|                          | Total<br>n = 54  | Birth Weight SDS         |                       |
|--------------------------|------------------|--------------------------|-----------------------|
|                          |                  | $\geq -1.5$ SD<br>n = 42 | $< -1.5$ SD<br>n = 12 |
| Birth weight SDS         | $-0.6 \pm 0.2^*$ | $-0.1 \pm 0.1$           | $-2.2 \pm 0.2$        |
| Target height SDS        | $-0.9 \pm 0.1^*$ | $-0.9 \pm 0.1$           | $-0.9 \pm 0.3$        |
| Onset of puberty (B2)    |                  |                          |                       |
| Chronological age (y)    | $8.6 \pm 0.1$    | $8.6 \pm 0.1$            | $8.6 \pm 0.1$         |
| Bone age (y)             | $9.8 \pm 0.1$    | $9.7 \pm 0.2$            | $10.0 \pm 0.2$        |
| Height (cm)              | $131.9 \pm 1.2$  | $132.8 \pm 1.4$          | $128.6 \pm 2.7$       |
| BMI (kg/m <sup>2</sup> ) | $18.2 \pm 0.3$   | $18.1 \pm 0.4$           | $18.7 \pm 0.7$        |
| Menarche (y)             | $12.2 \pm 0.2$   | $12.9 \pm 0.2$           | $11.3 \pm 0.3\#$      |
| Final height             |                  |                          |                       |
| Height (cm)              | $157.2 \pm 0.9$  | $158.3 \pm 1.0$          | $153.0 \pm 1.8\#$     |
| Height SDS               | $-0.8 \pm 0.1$   | $-0.6 \pm 0.2$           | $-1.5 \pm 0.3\#$      |
| Adjusted height SDS      | $0.1 \pm 0.1$    | $0.3 \pm 0.2$            | $-0.6 \pm 0.2\#$      |

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).

#  $P \leq .01$  versus girls with birth weight  $\geq -1.5$  SD.

12. de la Puente ML, Canela J, Alvarez J, Salleras L, Vicens-Calvet E. Cross-sectional study of the child and adolescent population of Catalonia (Spain). *Ann Hum Biol.* 1997;24:435–452
13. Ibáñez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism and ovarian hyperandrogenism in girls: relation to reduced fetal growth. *J Clin Endocrinol Metab.* 1998;83:3558–3662
14. Greulich WW, Pyle SI. *Radiographic Atlas of Skeletal Development of the Hand and Wrist.* Stanford, CA: Stanford University Press; 1959
15. Fokstuen S, Ginsburg C, Diplrernat, Zachmann M, Schinzel A. Maternal uniparental disomy 14 as a cause of intrauterine growth retardation and early onset of puberty. *J Pediatr.* 1999;134:689–695
16. Achermann JC, Hamdani K, Hindmarsh PC, Brook CGD. Birth weight influences the initial response to growth hormone treatment in growth-insufficient children. *Pediatrics.* 1998;102:342–345
17. de Zegher F, Francois I, van Helvoirt M, Beckers D, Ibáñez L, Chatelain P. Growth hormone treatment of short children born small for gestational age. *Trends Endocrinol Metab.* 1998;9:233–237
18. Cacciari E, Zucchini S, Cicognani A, et al. Birth weight affects final height in patients treated for growth hormone deficiency. *Clin Endocrinol.* 1999;51:733–739
19. Ibáñez L, Potau N, Enriquez G, de Zegher F. Reduced uterine and ovarian size in adolescent girls born small for gestational age. *Pediatr Res.* 2000;47:575–577
20. Ibáñez L, Potau N, de Zegher F. Ovarian hyporesponsiveness to follicle stimulating hormone in adolescent girls born small for gestational age. *J Clin Endocrinol Metab.* 2000;85:2624–2626

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

Lourdes Ibáñez, Angela Ferrer, Maria Victoria Marcos, Francisco Rodriguez Hierro and Francis de Zegher

*Pediatrics* 2000;106:e72

DOI: 10.1542/peds.106.5.e72

### Updated Information & Services

including high resolution figures, can be found at:  
<http://pediatrics.aappublications.org/content/106/5/e72>

### References

This article cites 19 articles, 4 of which you can access for free at:  
<http://pediatrics.aappublications.org/content/106/5/e72#BIBL>

### Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):  
**Endocrinology**  
[http://www.aappublications.org/cgi/collection/endocrinology\\_sub](http://www.aappublications.org/cgi/collection/endocrinology_sub)  
**Puberty**  
[http://www.aappublications.org/cgi/collection/puberty\\_sub](http://www.aappublications.org/cgi/collection/puberty_sub)  
**Chapters Views & News**  
[http://www.aappublications.org/cgi/collection/chapters\\_views\\_news](http://www.aappublications.org/cgi/collection/chapters_views_news)

### Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://www.aappublications.org/site/misc/Permissions.xhtml>

### Reprints

Information about ordering reprints can be found online:  
<http://www.aappublications.org/site/misc/reprints.xhtml>

# American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Lourdes Ibáñez, Angela Ferrer, Maria Victoria Marcos, Francisco Rodriguez Hierro and Francis de Zegher

*Pediatrics* 2000;106:e72

DOI: 10.1542/peds.106.5.e72

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/106/5/e72>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2000 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

