Pubertal course of persistently short children born small for gestational age (SGA) compared with idiopathic short children born appropriate for gestational age (AGA)

Liora Lazar, Uri Pollak 1, Ofra Kalter-Leibovici 2, Athalia Pertzelan and Moshe Phillip

Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, 2 Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer and 1 Faculty of Medicine, Ben Gurion University of the Negev, Beer Sheva, Israel

(Correspondence should be addressed to M Phillip; Email: mosheph@post.tau.ac.il)

(L Lazar and U Pollak contributed equally to this work)

Abstract

Objective: Few data are available on the pubertal development of children born small for gestational age (SGA) who fail to show catch-up growth.

Design: A longitudinal analysis compared the pubertal course of persistently short children born SGA compared to children with idiopathic short stature who were appropriate for gestational age (AGA).

One hundred and twenty-eight short children (height SDS, -1.7), including 76 (31 boys) born SGA and 52 (22 boys) born AGA, were regularly followed from early childhood to completion of puberty.

Results: Puberty was attained at normal age (10.5 – 14 years in boys, 9.5 – 13 years in girls) for most children in both the SGA and AGA groups (boys, 80% and 77%; girls, 76% and 78% respectively). The duration of puberty was similar in the SGA and AGA groups. Menarche occurred at normal age range but was significantly earlier in the SGA girls (P < 0.01 by ANOVA). Despite the similar total pubertal growth, the patterns of growth differed significantly: SGA group – accelerated growth and bone maturation rates from onset of puberty with peak height velocity at Tanner stages 2 – 3, followed by a decelerated growth rate and earlier fusion of the epiphyses; AGA group – steady progression of bone elongation and maturation throughout puberty (pubertal growth, P < 0.05 in both sexes; bone maturation, P < 0.001 in both sexes). Final height in the SGA group was compromised compared with their target height (P < 0.001).

Conclusion: Children born SGA have a normal pubertal course with a distinct pubertal growth pattern. This pattern may represent an altered regulation of their growth modalities.

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Introduction

The adaptation of the fetus to conditions of undernutrition in utero involves an alteration in endocrine set-points in the insulin, insulin-like growth factor (IGF) and growth hormone (GH) pathways. These are also maintained postnatally (1, 2) and may affect the long-term pattern of postnatal growth and development. A number of longitudinal studies have shown that although the majority of children born small for gestational age (SGA) exhibit significant catch-up growth during the first 6–12 months of life, about 10–17% do not. They tend to grow parallel to but below the normal centiles throughout childhood with no improvement during puberty, and they attain a final height (FHT) that is far below their genetic target height (THt) (3–6). The contribution of the pubertal process and the impact of pubertal growth on FHT in children born SGA remain unclear (4, 7–12), and the question of whether the in utero changes affect not only growth but also the pubertal process is still open. Most researchers report that puberty in these children is attained at a normal age or slightly earlier, and that their total pubertal growth and peak height velocity are normal. However, the bulk of these data were collected from cross-sectional studies that investigated the natural history of growth in children born SGA, but did not focus on the pubertal course. Furthermore, it is well established that subnormal growth during infancy or childhood has an impact on pubertal growth (13), yet the study samples included both children who exhibited catch-up growth with normalization of pre-pubertal height and children who remained short at 2 years of age and thereafter.

Since 1975, the Institute for Endocrinology and Diabetes of what is now the Schneider Children’s Medical Center of Israel has been following a large group of children born SGA who were referred because
of a failure to show sufficient catch-up growth. The aim of the present study was to characterize the data on the pubertal onset, course and growth of these children and to compare the findings with those of children with idiopathic familial short stature who were appropriate for gestational age (AGA) at birth.

Subjects and methods

Patients

The study group included 128 short children drawn from a large population of short children referred to our endocrine clinic between the years 1975 and 1990. Seventy-six children (31 boys and 45 girls) were born SGA, defined as a birth weight below $-2$ S.D. for gestational age (14), and 52 (22 boys and 30 girls) had normal birth size for gestational age (15) (Table 1). Six children in the SGA group and four in the AGA group were born before term (gestational age 35–36 weeks), but their perinatal course was uneventful. There was no documentation of maternal disorders or abnormalities throughout pregnancy (specifically, heavy smoking, alcohol abuse or hypertension) in either the AGA or SGA group. Eight mothers (five in the SGA group and three in the AGA group) developed pre-eclampsia a few days prior to delivery. Selection for the study was based on the following criteria: inclusion – available information on gestational age and weight at birth; persistent short stature (height SDS below $-1.7$ for chronological age) with no catch-up growth during infancy and childhood (chronological age 2.5–4 years); documented age and auxological data at onset of puberty; regular follow-up since childhood to completion of puberty; exclusion – presence of endocrinological or chronic diseases such as chronic renal failure, severe bronchial asthma with regular steroid treatment, inflammatory bowel disease and celiac disease; neurological handicap; previous or ongoing chemotherapy; chromosomal aberrations; malformation syndromes including dysmorphic features characteristic of Russel–Silver syndrome; and skeletal dysplasia. Although receipt of treatment interfering with growth and puberty was not one of the exclusion criteria, it was not relevant, as none of the children developed precocious puberty, and early puberty is not an indication for treatment. Furthermore, the children in whom puberty was delayed had already been progressing spontaneously to puberty at the ages when sex steroids would be indicated for induction of puberty (boys > 15 years; girls > 13 years). Therefore, no growth-related treatment was presented for any of the patients.

Stringent conditions were applied so that a longitudinal analysis of the pubertal course could be conducted in a relatively large sample despite the retrospective design of the study. The final cohort was representative of the two groups (SGA and AGA), as the dropouts differed from the participants only in lack of continuous follow-up.

Methods

Birth and perinatal data were taken from the medical records. Birth weight SDS for gestational age was calculated according to the tables of Usher and McLean (15). During the pre-pubertal period, height, weight and pubertal stage were determined at 4–12-month intervals. During puberty, all the children were followed every 3–4 months. For purposes of comparison of both sexes at different ages, body mass index (BMI) (weight in kilograms/height in $m^2$) was calculated and BMI values were converted into SDS using the updated American CDC reference values (16).

Pubertal stage was assessed at every visit according to the method of Marshall and Tanner (17, 18). At each pubertal stage, the advancement of pubarche (degree of sexual hair) and gonadarche (testicular volume in boys and stage of breast development in girls) was classified separately. Onset of puberty was categorized by the age at which pubertal signs (gonadarche with or without pubarche) appeared, as follows: precocious puberty – before age 8 years in girls and 9 years in boys (19, 20); early puberty – ages 8–9.5 years in girls and 9–10.5 years in boys (the maximum cut-off ages in girls and boys correspond to $-2$ S.D. below the average age of pubertal onset) (20); average puberty – ages 9.5–13 years in girls and 10.5–14 years.
years in boys: delayed puberty — beyond the age of 13 years in girls and 14 years in boys (19–21). Precocious pubarche was defined as the appearance of sexual hair only before age 8 years in girls and 9 years in boys (19, 20). Pubertal rate was estimated by the duration of transition from Tanner stages 2 to 5. A duration of less than 2.5 years was considered fast puberty and of more than 4 years, slow puberty (19, 20). Total pubertal growth was calculated as the difference between height at completion and onset of puberty. We applied this criterion to the whole cohort for purposes of consistency, as all the children were followed until completion of puberty, and all the girls but only some of the boys were followed to FHt. The peak height velocity (maximal growth rate during puberty) was analyzed as the highest growth rate (measured every 3 months throughout puberty) over a complete 1-year period and was related to the pubertal stage at its occurrence.

Bone age (BA) was estimated according to the Atlas of Greulich and Pyle (22) every 1–2 years throughout the pre-pubertal period, and during puberty when clinical evaluation revealed a transition of the pubertal stage. FHt was determined when growth velocity dropped to less than 2.0 cm/year and BA was beyond 15 years in girls and 17 years in boys. Predicted final height (FHt) was calculated by the method of Bayley and Pinneau (23) using the average tables for both boys and girls. THt, the corrected mid-parental height, was calculated according to Tanner et al. (24).

Analysis of all the available auxological characteristics (height, BMI and BA) was performed in all children at early childhood (last measurement between ages 2.5 and 4 years), at onset of puberty, at each pubertal stage (defined by gonadarche), and at FHt. Longitudinal analysis of growth and bone maturation rates was carried out throughout puberty.

All clinical and radiological evaluations were performed by the same team, comprising pediatric endocrinologists and nurses. Tanner staging was performed by the same three senior pediatric endocrinologists, among whom interpreter consistency was validated.

The data on basal and stimulated levels of gonadotropins, adrenal androgens and sex hormones were not analyzed because the blood tests were not performed consistently at regular periods throughout puberty. However, the hormone levels of those children who did undergo blood testing were within the normal range for the various pubertal stages. It is of note that the decision regarding hormonal testing was made by the medical consultant on an individual basis in children with either early or delayed puberty. These tests were not contributory and did not effect a change in diagnosis. Hence, they did not constitute a bias in the cohort selection.

### Statistical analysis

The BMDP program (25) was used for the statistical analyses. Values are expressed as means ± S.D. Comparisons between groups were carried out using ANOVA and ANOVA with repeated measures to test for changes over time. Stepwise multiple regression analysis was applied to evaluate the effect of various early pre-pubertal parameters (birth weight, height, BMI and BA) on age at onset of puberty and on pubertal growth spurt.

### Results

The clinical characteristics of the SGA and AGA groups at birth are shown in Table 1, and in early childhood in Table 2.

The chronological age (CA), the BA delay over CA (CA minus BA), and the BMI SDS in early childhood were remarkably similar in the two groups. The height SDS (Ht SDS) of both groups was approximately −1.8 to −1.7 throughout early childhood.

Age at onset of puberty was significantly lower in the children born SGA than in the children born AGA.

### Table 2 Early childhood and early pubertal auxological data of 128 short children, 76 born SGA (31 boys and 45 girls) and 52 born AGA (22 boys and 30 girls). Values are means ± S.D.

<table>
<thead>
<tr>
<th>Boys</th>
<th>Early childhood</th>
<th>Onset of puberty</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>SGA</td>
<td>AGA</td>
</tr>
<tr>
<td>CA (years)</td>
<td>3.4±0.6</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td>CA – BA (years)</td>
<td>2.6±1.0</td>
<td>2.7±0.9</td>
</tr>
<tr>
<td>Ht SDS</td>
<td>−1.8±0.4</td>
<td>−1.7±0.2</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>−0.4±0.2</td>
<td>−0.3±0.5</td>
</tr>
<tr>
<td>Girls</td>
<td>Early childhood</td>
<td>SGA</td>
</tr>
<tr>
<td></td>
<td>SGA</td>
<td>AGA</td>
</tr>
<tr>
<td>CA (years)</td>
<td>3.6±0.8</td>
<td>3.3±0.6</td>
</tr>
<tr>
<td>CA – BA (years)</td>
<td>1.9±0.7</td>
<td>2.0±1.0</td>
</tr>
<tr>
<td>Ht SDS</td>
<td>−1.8±0.4</td>
<td>−1.8±0.5</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>−0.4±0.8</td>
<td>−0.4±0.5</td>
</tr>
</tbody>
</table>

NS = not significant.

* Significance of difference between SGA and AGA, for each parameter.
(P < 0.01 for both sexes). However, comparison of the age distribution histograms (Fig. 1) revealed that although the SGA group had a higher prevalence of early puberty than the AGA group (for boys, 13% vs 5%; for girls, 20% vs 3%), and a lower prevalence of delayed puberty (for boys, 7% vs 18%; for girls 4% vs 19%), most of the boys and girls of both groups attained puberty at a normal age (for boys, 80% of the SGA group vs 77% of the AGA group; for girls, 76% vs 78% respectively). None of the children, either SGA or AGA, developed precocious puberty.

Multiple regression analysis showed that the only pre-pubertal predictor of age at onset of puberty was birth weight SDS. However, only a small percentage of the variance was explained by this parameter (r = 0.27). No correlation was found between age at onset of puberty and any of the other pre-pubertal variables: gestational age, height, BMI, and BA delay over CA.

Analysis of the auxological data at onset of puberty (Table 2) showed that the BA of the boys and girls in the SGA group was significantly more advanced than that of the AGA children (P < 0.001 for boys and girls). Their Ht SDS and BMI SDS were also higher (P < 0.01 and P = 0.05 respectively for both boys and girls).

Menarche occurred within the normal age range in both groups, but significantly earlier in the SGA than the AGA group (P < 0.01) (Table 3).

Longitudinal analysis of the pubertal course (Table 3) yielded a similar mean duration of puberty in the two groups. Mean total pubertal growth and the peak height velocity were also similar. On stepwise regression analysis using total pubertal growth as an independent variable and age at onset of puberty and group (SGA or AGA) as dependent variables, total pubertal growth was negatively correlated with age at onset of puberty in both boys and girls (r² = 0.42 and 0.41 respectively). However, being in the SGA or the AGA group did not correlate with total pubertal growth, either in the boys or in the girls. Yet, the pattern of pubertal growth (analyzed using ANOVA with repeated measurements) was significantly different between the SGA and the AGA groups (Fig. 2). In both boys and girls, there was a significant statistical interaction between the SGA and the AGA groups for height gain (P < 0.05) (Fig. 2A and B) and absolute height changes (P < 0.05) (Fig. 2C and D). The SGA group reached peak height velocity at an earlier pubertal stage (Tanner stage 3 for boys and stage 2 for girls) than the AGA group (Tanner stages 4–5 and 3–4 respectively). This early acceleration was followed by a deceleration toward completion of puberty, with Ht SDS dropping back to −1.6 SDS. In the AGA group, the height gain of the boys improved continuously to

![Figure 1](https://example.com/figure1.png)  
**Figure 1** Distribution of age at onset of puberty in 76 short children born SGA (31 boys, 45 girls) compared with 52 short children born AGA (22 boys, 30 girls).

<table>
<thead>
<tr>
<th>Table 3 Pubertal course in 128 short children, 76 born SGA and 52 born AGA. Values are means ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Duration P2–P5 (years)</td>
</tr>
<tr>
<td>TPG (cm)</td>
</tr>
<tr>
<td>PHV (cm)</td>
</tr>
<tr>
<td>(At pubertal stage)</td>
</tr>
<tr>
<td>Menarche ages (years)</td>
</tr>
</tbody>
</table>

* Significance of difference between SGA and AGA, for each parameter.
Figure 2 Growth and bone maturation rates in 76 short children born SGA (31 boys, 45 girls) compared with 52 short children born AGA (22 boys, 30 girls) followed longitudinally throughout puberty. P1 – early childhood; P2, P3, P4 and P5 – pubertal stages according to Tanner.
completion of puberty, and the height gain of the girls was steady at each pubertal stage (Fig. 2A and B). Therefore, by completion of puberty, the significant earlier difference in Ht SDS between the groups disappeared (Fig. 2C and D).

The rate of bone maturation from Tanner stages 2 to 5 also demonstrated a highly significant different interaction over time between the two groups (for both boys and girls, \( P < 0.001 \)) (Fig. 2E and F). In the boys, BA was delayed in childhood and at onset of puberty. Thereafter, in the SGA boys, bone maturation accelerated, leading to a significant decrease in BA delay over CA, starting already in Tanner stages 2 and 3, whereas in the boys born AGA, advancement of BA was observed only towards Tanner stage 4. In the girls born SGA, BA was already more advanced and corresponded to CA at onset of puberty. Thereafter, BA advanced steadily over time. In the girls born AGA, delayed BA was observed in the early stages of puberty, and advancement occurred only towards Tanner stages 4 and 5.

All 15 girls, but only 15 boys (SGA, 8; AGA, 7), were followed to FHt. The remaining boys were followed to completion of puberty. We considered their PFHt at Tanner stage 5 as their FHt; since by that time, their BA was 15.5–16 years, at which point the PFHt is accurate in both boys with a normal growth pattern as well as short boys, either SGA or AGA, with early or delayed puberty (23, 26).

The FHt of the children in the two groups was not significantly different (Table 4). After adjusting for THt, we noted a significant deficit in FHt in the SGA group (for boys, \( P < 0.01 \); for girls, \( P < 0.001 \)), but not in the AGA group were FHt and THt were similar. THt was significantly greater in the SGA than the AGA group (for boys, \( P < 0.01 \); for girls, \( P < 0.001 \)).

**Discussion**

This is, to the best of our knowledge, one of the first longitudinal studies providing information on the pattern of pubertal development and pubertal growth of persistently short children born SGA. The major finding of the study was that the pattern of growth in short children born SGA is distinct from that in children born AGA, with peak height velocity occurring at an earlier pubertal stage despite the similar total pubertal growth of the two groups.

There are several limitations to this study. We selected only those patients who were followed over the long term. Therefore, this cohort is not representative of the whole SGA and AGA population. Nevertheless, this is a relatively large uniform sample with clear differences between the SGA and AGA groups. Secondly, as the data were collected retrospectively, not all the boys were followed to FHt. However, as all completed puberty (Tanner stage 5) we were able to use their PFHt, which is accurate at bone age 15.5–16, as their FHt (23, 26). The mean age at onset of puberty was within the normal range in the SGA group (boys, 12.0±0.9; girls, 10.4±1.5), albeit significantly lower than in the AGA group (\( P < 0.01 \)). Although one study reported delayed pubertal onset in children born SGA compared with controls (27), all other researchers had similar findings to ours. They attributed this difference to the relatively early puberty in all children born SGA compared with the delayed puberty in most short children born AGA (7–9, 11). However, our data demonstrated a normal pubertal onset in the vast majority of children born SGA (80% of the boys, 76% of the girls), similar to the short children born AGA (77% of the boys, 78% of the girls). Only 13% of the boys and 20% of the girls born SGA had a relatively early puberty (onset at age 9–10.5 and 8–9.5 years respectively), while 18% of the boys and 19% of the girls born AGA had delayed puberty (onset of puberty beyond ages 14 and 13 years respectively). This small subset of patients might explain the statistically significant difference in mean age at onset of puberty between the whole SGA and AGA groups (\( P < 0.01 \) for both boys and girls) (Fig. 1, Table 2).

Some studies have suggested that children born SGA might be exposed to higher insulin levels due to the presence of insulin resistance beginning in the prenatal period. High insulin levels could, later in life, stimulate early secretion of luteinizing hormone, leading to early puberty (2, 28, 29). Nevertheless, in most of the

**Table 4** FHt compared with THt in 128 short children, 76 born SGA and 52 born AGA. Values are means±S.D.

<table>
<thead>
<tr>
<th></th>
<th>SGA</th>
<th>AGA</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>31†</td>
<td>22‡</td>
<td></td>
</tr>
<tr>
<td>FHt (cm)</td>
<td>169.5±5.1</td>
<td>168.3±4.0</td>
<td>NS</td>
</tr>
<tr>
<td>THt (cm)</td>
<td>173.9±5.2</td>
<td>167.5±3.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( P ) value*</td>
<td>&lt; 0.01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>45</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>FHt (cm)</td>
<td>153.6±5.7</td>
<td>152.8±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>THt (cm)</td>
<td>162.9±5.2</td>
<td>153.7±5.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( P ) value*</td>
<td>&lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant.

* Significance of difference between SGA and AGA, for each parameter.
† Actual FHt, \( n = 8 \); predicted FHt at completion of puberty, \( n = 23 \).
‡ Actual FHt, \( n = 7 \); predicted FHt at completion of puberty, \( n = 15 \).
children born SGA in our sample, the course and timing of puberty were within the normal range. This finding may place doubt on the role of the uterine environment on hormone secretion at puberty (19, 30). Despite the comparable rate of development of gonadarche in the children of both groups, in the girls born SGA, menarche, though occurring at an adequate age, was significantly earlier than in the girls born AGA \((P < 0.01)\). This finding is in agreement with the study of Ibanez \textit{et al.} (31).

The similar total pubertal growth and peak height velocity magnitude in the short SGA and AGA children implies an appropriate pubertal growth spurt in children born SGA. This finding is in agreement with the study of Leger \textit{et al.} (9), who claimed that puberty has no influence on final height outcome in these children, as their pubertal spurt is adequate. Nevertheless, the FHt of the SGA group was compromised (Table 4). One possible explanation for this finding may be a slower than expected growth spurt. There is a well-known negative relationship between total pubertal growth and age of pubertal onset (30). Since the mean age at onset of puberty in our SGA group was 1 year earlier than in the AGA group, their growth spurt should have been larger. Indeed, we found that age at pubertal onset was negatively associated with pubertal growth spurt in children of both groups. However, no correlation was demonstrated between the pubertal growth spurt and belonging to either the SGA or the AGA group. This discrepancy may also be related to the similar age at onset of puberty in the majority of children born either SGA or AGA.

Another possible explanation for this finding may lie in the pattern of their pubertal growth. In contrast to a previous report (12), all the children born SGA in our series demonstrated growth acceleration from onset of puberty, with early peak height velocity at Tanner stage 3 in boys and Tanner stage 2 in girls (Fig. 2), compared with Tanner stages 4–5 in boys and 3–4 in girls of the AGA group, and in children with normal puberty (19, 20). The early growth acceleration yielded an improvement in HT SDS, which proved to be transient, as growth deceleration occurred from mid-puberty to FHt, with a drop back to the previous height percentiles (Fig. 2). Other authors have also suggested that children born SGA show less pubertal growth than expected, being that their peak height velocity, though occurring earlier than in children with AGA, is not more pronounced (11).

The accelerated bone elongation was accompanied by an accelerated bone maturation rate and early fusion of the growth plates (Fig. 2E and F). These findings are in accordance with previous reports on bone maturation of children born SGA (7, 8, 11). By contrast, the short children born AGA exhibited gradual growth acceleration and bone maturation rates throughout puberty, with an appropriate progression of BA.

The pathophysiologic mechanism underlying the unique pubertal growth pattern of children born SGA remains unclear. It is well established that the regulation of the insulin, GH and IGF-I pathways and the sensitivity of their receptors are altered by the abnormal prenatal environment of children born SGA (1, 2, 32–34). Perhaps the sex hormone receptors in the growth plate are altered as well. This would result in a different response to normal hormonal stimulations and lead to unusual pubertal growth.

Conclusions

Children born SGA with persistent short stature demonstrate a similar timing and course of pubertal development to normal children, and to short children born AGA. This finding may imply an intact hypothalamic–pituitary–gonadal axis. However, their FHt is compromised, perhaps due to their distinct pattern of pubertal growth, characterized by an early acceleration followed by a relatively early deceleration in association with early fusion of the epiphyses, which may result from altered regulation of growth modalities.

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References