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Puberty in Growth Hormone-Treated Children Born Small for Gestational Age (SGA)

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Seventy-five small for gestational age (SGA) children were studied in a randomized, double-blind, dose-response GH trial with either 1 or 2 mg GH/m^2·d. Mean (SD) age at the start of GH therapy was 7.3 (2.2) yr. Data were compared with Dutch reference data.

In SGA boys, mean (SD) age at onset of puberty was 12.0 (1.0) and 11.6 (0.7) yr, and in SGA girls it was 10.9 (1.1) and 10.6 (1.2) yr when treated with 1 and 2 mg GH/m^2·d, respectively. SGA boys treated with the lower GH dose started puberty later than the appropriate for gestational age (AGA) controls; for the other GH-dosage groups there was no significant difference in age at onset of puberty compared to AGA controls. The age at menarche and the interval between breast stage M2 and menarche were not significantly different for GH-treated SGA girls compared to their peers. The duration of puberty and pubertal height gain of GH-treated SGA boys and girls were not significantly different between the two GH-dosage groups and were comparable with untreated short children born SGA.

In conclusion, long-term GH therapy in short SGA children has no influence on the age at onset and progression of puberty compared to AGA controls, regardless of treatment with a dose of 1 or 2 mg GH/m^2·d. Duration of puberty and pubertal height gain were not significantly different between the GH-dosage groups. (*J Clin Endocrinol Metab* 88: 5753–5758, 2003)

SPONTANEOUS POSTNATAL CATCH-UP growth occurs in most infants born SGA, but about 10% remain short after the age of 2 yr (1, 2). Important determinants of final height are the height and age at onset of puberty and the magnitude and duration of the pubertal growth (3–5). Data on puberty in children born SGA are limited. Most studies deal with height and age at onset of puberty and not with duration and progression of puberty. Moreover, study results are difficult to compare due to the various definitions of SGA and the various definitions used for the milestones of puberty. Persson *et al.* (6) reported that children born SGA were shorter at onset of puberty than their peers but that the age at onset was the same. A French study reported that the age at onset of puberty, the age at menarche, and the pubertal growth spurt in girls born SGA were comparable with the normal population (7, 8). A Swedish population-based study showed that in SGA children with a spontaneous catch-up growth, puberty occurred at the normal age in contrast to SGA children with persistent short stature who had a slightly earlier pubertal onset (1). Most authors do seem to agree that puberty in short SGA children starts at a normal age, but relatively early for their short stature (9).

Several studies have demonstrated that GH treatment results in a significant catch-up growth in short prepubertal SGA children (10, 11). However, only very limited data are available on puberty and pubertal growth of children born SGA who have been treated with GH for several years. We therefore evaluated puberty in terms of age and height at onset of puberty, age at menarche, interval between breast development and menarche, duration of puberty, and pubertal height gain in 75 GH-treated children born SGA who participated in a randomized, double-blind, dose-response trial, evaluating the effect of a GH dose of either 1 or 2 mg/m^2·d (0.03 or 0.07 mg/kg·d), in comparison to normal-statured children born appropriate for gestational age (AGA).

Abbreviations: AGA, Appropriate for gestational age; AH, adult height; BMI, body mass index; CI, confidence interval; P10, 10th percentile; P50, 50th percentile; P90, 90th percentile; RUS, radius, ulna, short-bones score; SDS, SD score; SGA, small for gestational age; TH, target height.

Patients and Methods

Study group

The study group consisted of 75 prepubertal short children born SGA who met the following criteria at the start of GH treatment: 1) birth length SD score (SDS) below −2 SD for gestational age according to the standards of Usher and McLean (12); 2) chronological age between 3 and 11 yr in boys and 3 and 9 yr in girls at the start of the study; 3) height SDS for chronological age below −2 SD according to Dutch references (13); 4) height velocity SDS for chronological age no greater than zero (13, 14), to exclude children with spontaneous catch-up growth; 5) prepubertal stage defined as Tanner breast stage I for girls, and testicular volume less than 4 ml for boys (15); 6) uncomplicated neonatal period, that is without signs of severe asphyxia (defined as an Apgar score <3 after 5 min), without sepsis neonatorum and without long-term complications of respiratory ventilation such as bronchopulmonary dysplasia. Exclusion criteria were: endocrine or metabolic disorders, chromosomal disorders, growth failure caused by other disorders (emotional deprivation, severe chronic illness, chondrodysplasia) or syndromes, and previous or present use of medication that could interfere with GH treatment. The original group consisted of 79 children. Four children dropped out of the study before the onset of puberty for the following reasons. Three children were no longer motivated to inject GH daily after 15, 45, and 51 months of GH treatment, respectively, despite ongoing catch-up growth with GH treatment. In one prepubertal boy, GH treatment was discontinued after 27 months because of signs of GH insensitivity. Because these four children were lost to follow-up after discontinuation of GH, their data were not included in the analysis.

Four centers in The Netherlands participated in the study. The study was approved by the Ethics Committee of each participating center. Due to ethical considerations, the Ethics Committees did not allow for a control group until adult height (AH). Written informed consent was obtained from the parents or custodians of each child.

Study design

All children were randomly and blindly assigned to one of two GH-dosage groups: group A received 1 mg GH /m^2·d, and group B received 2 mg GH/m^2·d (~0.03 or 0.07 mg/kg·d, respectively). Biosynthetic GH (recombinant human GH; Norditropin, Novo Nordisk A/S, Denmark) was given sc once daily at bedtime with a pen injection (Nordiject 24). Every 3 months, the total GH dose was adjusted to the calculated body surface. The study was kept double-blind by using an equal volume of a reconstituted preparation (10).

Measurements

Height was measured at baseline and subsequently every 3 months, according to the method of Cameron, using a Harpenden stadiometer (16). Four measurements were made per visit by the same investigators (1991–1995, W. d. Waal; 1995–1998, T. Sas; and 1998–2001, Y. v. Pareren), and the mean was used for the analysis. Height was expressed as SDS for chronological age (13). Target height (TH) was calculated on the basis of Dutch reference data with the addition of 3 cm for a secular trend: for boys, ½ × ($Height_{father}$ + $Height_{mother}$ + 12) + 3; for girls, ½ × ($Height_{father}$ + $Height_{mother}$ − 12) + 3 (13). TH and body mass index (BMI) were expressed as SDS using Dutch references (13). Bone age was determined by the same investigators according to Tanner and Whitehouse radius, ulna, short-bones score (RUS TW-2) (17). AH in GH-treated children was defined as the condition when height velocity had dropped less than 0.5 cm during the previous 6 months and the bone age was at least 15 yr for girls and at least 16.5 yr for boys. AH was reached either during GH treatment or during the 2-yr follow-up after discontinuation of GH treatment. GH treatment was discontinued after reaching AH or on the patient's decision at near-AH. At each visit, pubertal stages were assessed by the same investigators according to the method of Tanner and Whitehouse (15). The onset of puberty was defined as a breast development stage 2 according to Tanner scale for girls (15) and a testicular volume equal or more than 4 ml for boys as determined by means of a Prader orchidometer. At each 3-monthly visit, girls were asked if and when they had their menarche. The interval between breast development (M2) and menarche was defined as the time from onset of puberty (breast stage 2) until menarche. The pubertal height gain and the duration of puberty were defined as the AH minus height (centimeters) at onset of puberty and the time from onset of puberty until AH, respectively.

Statistical analyses

The Fourth Dutch National Growth Study (1997) served as reference for age and height at onset of puberty, age at menarche, and the interval between M2 and menarche of normal statured children born AGA (controls) (18). In that study, the same definitions for pubertal milestones were used as in our study, but because AH was not defined in the Dutch Growth Study we could not compare our data on duration of puberty and pubertal height gain with Dutch references. An independent statistician (P.M.) performed the statistical analyses. Data are expressed as the mean ± SD, unless indicated otherwise. The null hypothesis of mean SDS values being equal to zero was tested by the one-sample Student's *t* test. Mean differences of continuous variables between groups were tested using a Student's two-sample *t* test with variances pooled across all groups. The corresponding 95% confidence interval (CI) was used in case of no significance in the mean difference. Multiple linear regression analyses were used to test the influence of several variables on the age at onset of puberty, interval between M2 and menarche, and pubertal height gain in GH-treated SGA children. A P value < 0.05 was considered significant. All analyses were performed using SPSS version 10.0 (SPSS, Inc., Chicago, IL).

Results

GH trial

Table 1 lists the baseline clinical data of all 75 children at start of GH treatment. Both GH-dosage groups had similar initial characteristics at the start of GH treatment. After the onset of puberty, three children dropped out of the study: one girl due to early puberty at the age of 8.4 yr after 27 months of GH treatment, and two other children who were not motivated despite ongoing GH-induced catch-up growth. Their data were only included in the analysis of pubertal onset.

The onset of puberty

Table 2 lists the age, height (SDS), bone age, BMI (SDS), and duration of GH treatment at the onset of puberty for both GH-dosage groups compared with Dutch AGA controls. Mean (SD) age at onset of puberty for boys was 12.0 (1.0) yr in group A and 11.6 (0.7) yr in group B, and for girls 10.9 (1.1) yr in group A and 10.6 (1.2) yr in group B, without significant differences between the two GH-dosage groups. Boys of group A were significantly older at onset of puberty than the AGA controls. For girls the age at onset in the GH-dosage groups *vs.* the AGA controls was not significantly different. Mean height SDS at onset of puberty for boys was −1.3 (0.7) in group A and −0.9 (0.9) in group B, and for girls −1.0 (0.6) in group A and −0.9 (1.4) in group B, without significant differences between the two GH-dosage groups. Height SDS at onset of puberty was significantly lower than for the AGA controls, for boys and girls.

At onset of puberty, there was a moderately advanced bone age for boys and girls compared with age, regardless of GH-dosage group. However, only in boys was bone age significantly older than chronological age. The BMI SDS in boys and girls was significantly lower than zero for both GH-dosage groups without a significant difference between the two GH-dosage groups. The duration of GH treatment before the onset of puberty in boys and girls was not significantly different between the two GH-dosage groups.

Menarche

The mean age at menarche and the interval between M2 and menarche between the GH-dosage groups and the AGA controls were not significantly different (Table 3). In addition, age at menarche and the interval between M2 and menarche were not significantly different between both GH-dosage groups.

TABLE 1. Clinical data in 75 children at start of GH treatment

	Group A 1 mg/m^2·d (n = 39)	Group B 2 mg/m^2·d (n = 36)
Male/female	29/10	21/15
Gestational age (wk)	37.3 (3.2)	36.0 (4.2)
Birth length SDS	−3.5 (1.4)	−3.5 (1.6)
Birth weight SDS	−2.6 (1.2)	−2.6 (1.0)
Chronological age (yr)	7.4 (2.0)	7.3 (2.4)
Bone age (RUS; yr)	6.6 (2.5)	6.9 (3.0)
Height SDS	−3.0 (0.7)	−3.1 (0.7)

Data are expressed as mean (SD).

The duration of puberty and pubertal height gain

Forty-six children reached AH. Their baseline data were comparable with those of the 29 SGA children who did not yet reach AH, with the exception of an older mean age at start of GH treatment [8.5 (1.7) yr compared with 5.6 (1.7) yr in the 29 SGA children]. The duration of puberty and pubertal height gain were analyzed for those who reached AH (Table 4). The duration of puberty was not significantly different for group A and group B in both sexes. The mean (SD) pubertal height gain for boys was 27.0 (8.4) cm in group A and 31.4 (4.1) cm in group B, in girls 19.0 (7.3) cm in group A and 18.9 (5.7) cm in group B. For boys and girls, mean pubertal height gain was not significantly different between the two GH-dosage groups.

Figures 1 and 2 show the 10th percentile (P10), 50th percentile (P50), and 90th percentile (P90) ages of reaching the milestones of puberty for boys and girls, respectively.

Variables

Table 5 shows the results of the multiple regression analysis regarding the age at onset of puberty, interval between M2 and menarche, and pubertal height gain.

Variables influencing age at onset of puberty. Boys started their puberty 1 yr later than girls. The longer the duration of GH treatment, the older the age at the start of puberty. BMI and bone age delay at onset of puberty and GH dosage had no influence on the age at onset.

Variables influencing the interval between M2 and menarche. The older the age at onset of puberty, the shorter the interval

TABLE 2. Data at onset of puberty in 75 GH-treated SGA children *vs.* Dutch AGA controls

	SGA		Difference B − A (95% CI)	AGA controls[a]
	Group A	Group B		
Boys				
No.	29	21		2524
Age (yr)	12.0 (1.0)[b]	11.6 (0.7)	−0.4 (−0.9 to 0.1)	11.5
Height (cm)	144.7 (7.8)	145.2 (6.2)	0.5 (−3.7 to 4.6)	151.0
Height SDS	−1.3 (0.7)[c]	−0.9 (0.9)[c]	0.4 (0.0 to 0.9)	0.0
Bone age (RUS yr)	12.4 (2.8)	12.7 (1.2)	0.3 (−1.0 to 1.6)	
BMI SDS	−0.5 (1.3)	−0.3 (0.6)	0.2 (−0.4 to 0.8)	
Duration of GH therapy (yr)	4.3 (2.2)	4.0 (2.5)	−0.3 (−1.7 to 1.0)	
Girls				
No.	10	15		2266
Age (yr)	10.9 (1.1)	10.6 (1.2)	−0.3 (−1.2 to 0.7)	10.7
Height (cm)	141.9 (7.4)	141.5 (10.8)	−0.4 (−8.5 to 7.7)	147.3
Height SDS	−1.0 (0.6)[c]	−0.9 (1.4)[c]	0.1 (−0.7 to 1.0)	0.0
Bone age (RUS yr)	11.3 (1.4)	11.1 (1.6)	−0.2 (−1.5 to 1.1)	
BMI SDS	−0.8 (0.9)	−0.6 (0.8)	0.2 (−0.5 to 0.9)	
Duration of GH therapy (yr)	4.0 (1.9)	3.7 (1.8)	−0.3 (−1.9 to 1.2)	

Data are expressed as mean (SD). Groups A and B received 1 and 2 mg GH/m^2·d, respectively.
[a] Data of 4th Dutch National Growth Study (18).
[b] Group A *vs.* AGA controls, $P = 0.02$.
[c] SGA groups *vs.* AGA controls, $P < 0.05$.

TABLE 3. Age at menarche and interval between M2 and menarche in GH-treated SGA girls compared to Dutch AGA controls

	SGA		Difference B − A (95% CI)	AGA controls[a]
	Group A	Group B		
No.	10	13		3028
Age at menarche (yr)	12.9 (0.8)	13.1 (1.3)	0.2 (−0.7 to 1.2)	13.2
Interval M2 → menarche (yr)	2.0 (0.9)	2.3 (0.9)	0.3 (−0.5 to 1.1)	2.5

Data are expressed as mean (SD). Groups A and B received 1 and 2 mg GH/m^2·d, respectively.
[a] Data of 4th Dutch National Growth Study (18).

TABLE 4. Pubertal height gain and duration of puberty in 46 GH-treated SGA children who reached AH

	Group A 1 mg/m^2·d	Group B 2 mg/m^2·d	Difference B − A (95% CI)
Boys	n = 14	n = 12	
Duration of puberty (yr)	5.0 (1.3)	5.4 (0.8)	0.4 (−0.5 to 1.3)
Pubertal height gain (cm)	27.0 (8.4)	31.4 (4.1)	4.5 (−1.0 to 9.9)
TH SDS	−1.0 (0.9)	−0.5 (0.7)	0.5 (0.0 to 1.0)
Girls	n = 9	n = 11	
Duration of puberty (yr)	3.9 (1.0)	4.1 (1.1)	0.2 (−0.8 to 1.2)
Pubertal height gain (cm)	19.0 (7.3)	18.9 (5.7)	−0.1 (−6.2 to 6.1)
TH SDS	−0.7 (0.7)	−0.4 (1.1)	0.3 (−0.5 to 1.1)

Data are expressed as mean (SD).

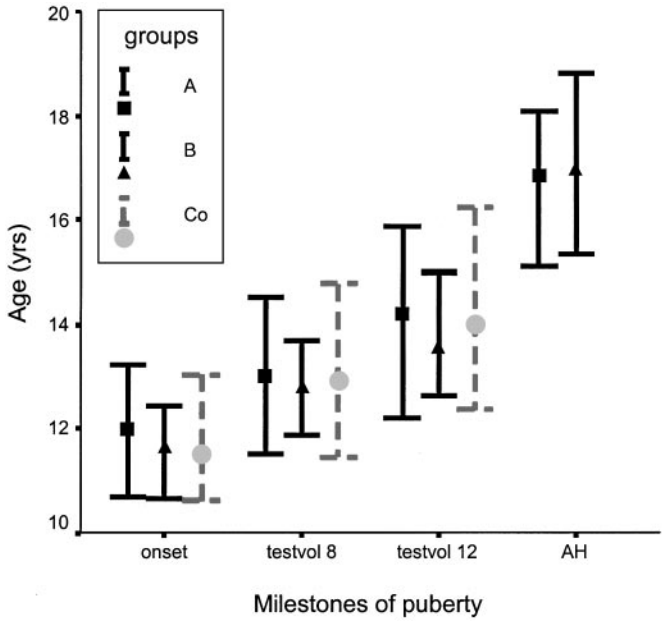

FIG. 1. Milestones of puberty for boys. P10, P50, and P90 ages of reaching the milestones of puberty for boys. onset, Onset of puberty; testvol 8, testicular volume of 8 ml [n = 28 (A), n = 20 (B)]; testvol 12, testicular volume of 12 ml [n = 26 (A), n = 20 (B)]; AH, adult height [n = 14 (A), n = 12 (B)]; Co, control.

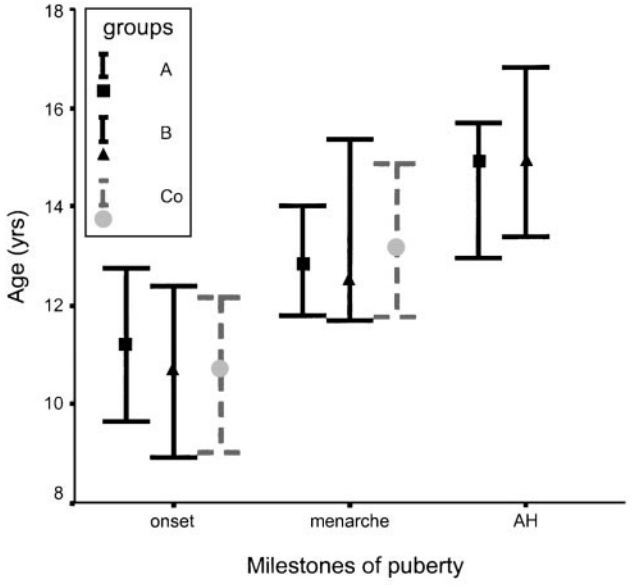

FIG. 2. Milestones of puberty for girls. P10, P50, and P90 ages of reaching the milestones of puberty for girls. onset, Onset of puberty; menarche, age at onset of menarche [n = 10 (A), n = 13 (B)]; AH, adult height [n = 9 (A), n = 11 (B)]; Co, control.

between M2 and menarche. A higher BMI resulted into a shorter interval, and the greater the bone age delay at onset of puberty the greater the interval. The GH dosage had no influence on the interval between M2 and menarche.

Variables influencing pubertal height gain. The difference in height gain between boys and girls was 13.8 cm. A greater bone age delay at onset of puberty increased pubertal height gain, and a taller height and older age at onset of puberty reduced the pubertal height gain. TH SDS and GH dosage had no significant effect on pubertal height gain.

Discussion

Our study presents the effects of GH treatment on puberty in short children born SGA. GH treatment with either 1 or 2 mg/m^2·d had no effect on pubertal onset, age at menarche, and interval between M2 and menarche, compared with Dutch reference data. Also, there was no GH-dose effect on the duration of puberty and pubertal height gain. Children with an older age, higher BMI, and smaller bone age delay at onset of puberty had a shorter interval between M2 and menarche. Again, the GH dose had no influence. The pubertal height gain was higher in children with a younger age, shorter height, and a greater bone age delay at onset of puberty, whereas the GH dose and TH had no effect on the pubertal height gain.

Our study shows that there is no GH-dose effect on the age at onset of puberty in SGA children. Also, GH-treated SGA children did not start puberty at a younger age compared with normal-statured Dutch children born AGA (18). SGA boys receiving 1 mg GH /m^2·d started their puberty even significantly later than normal-statured Dutch boys born AGA. Thus, GH treatment does not result into a younger age at onset of puberty, which is also supported by data of regression analysis, showing that the longer the duration of GH treatment, the later the onset of puberty. Both GH-dosage groups had a similar duration of GH treatment before the onset of puberty. Bone age delay and BMI had no influence on the age at onset of puberty. Our study also shows that SGA boys start their puberty 1 yr later than SGA girls, which is comparable with the Dutch reference data (18). Compared with published data of untreated SGA children, we did not find a significant difference regarding age at onset of puberty between our GH-treated SGA girls and Swedish untreated SGA girls (6). Boys receiving 2 mg were 0.8 yr ($P < 0.01$) younger at onset of puberty than untreated Swedish SGA boys. However, in this respect it is important to mention that the definition of onset of puberty in the Swedish study was different from ours, because their onset of puberty was defined as the moment at which the growth velocity starts to be more than 6 cm/yr, whereas for our study the onset of puberty was defined as a testis volume of 4 ml in boys, which is known to precede the pubertal growth velocity by 1 yr in boys. This means that when we would have applied the Swedish definition of puberty on our data set, the onset of puberty in our group would have been even later. In our study, we could not use the increase in growth velocity as the onset of puberty, because we could not determine whether the increase of height velocity was induced by GH therapy or pubertal growth spurt or both.

Height at onset of puberty was not significantly different in both GH-dosage groups, but it was significantly shorter than the height at pubertal onset of the Dutch normal-statured AGA children.

Boys had a significantly advanced bone age at onset of puberty compared with the chronological age in both GH

TABLE 5. Multiple regression analysis on age at onset of puberty (yr), interval between M2 and menarche (yr), and pubertal height gain (cm)

Dependent variable	Independent variable	Regression coefficient	SE	*P*
Age at onset of puberty	Sex (girls)	−1.04	0.24	<0.001
	Duration GH therapy at onset of puberty (yr)	0.13	0.06	0.02
	BMI SDS at onset of puberty	0.02	0.06	ns
	Bone age delay at onset of puberty (yr)	0.20	0.12	ns
	GH dose 1 *vs.* 2 mg/m^2·d	−0.25	0.22	ns
Interval M2 → menarche	Age at onset of puberty (yr)	−0.52	0.15	0.002
	BMI SDS at onset of puberty	−0.37	0.11	0.003
	Bone age delay at onset of puberty (yr)	0.32	0.14	0.03
	GH dose 1 *vs.* 2 mg/m^2·d	0.45	0.28	ns
Pubertal height gain	Sex (girls)	−13.78	1.60	<0.001
	Bone age delay at onset of puberty (yr)	2.60	0.33	<0.001
	Height at onset of puberty (cm)	−0.38	0.16	0.02
	Age at onset of puberty (yr)	−2.68	1.17	0.03
	TH SDS	1.17	0.78	ns
	GH dose 1 *vs.* 2 mg/m^2·d	2.25	0.14	ns

ns, Not significant.

groups. It is known that the bone maturation in children born SGA is different from the normal population and not a reliable estimation in SGA children (19–22). In addition bone age assessment by RUS TW-2 generally results in a 1 yr older bone age compared with Greulich and Pyle and the chronological age (23). Furthermore, it might be that GH treatment resulted in an acceleration of bone age in boys. However, it appears that the chronological age at onset of puberty and the progression of pubertal development of the GH-treated SGA boys and girls were not significantly different from normal-statured children born AGA.

One of the milestones of puberty in girls is menarche. Our study shows that the age at menarche and the interval between M2 and menarche, an indicator for the progression of puberty in girls, between both GH-dosage groups were not significantly different and were comparable with the age of Dutch AGA controls. The age at menarche and the interval between M2 and menarche were also not significantly different compared with Swedish untreated SGA girls. This suggests that GH treatment has no influence on the progression of puberty in girls. An older age, higher BMI, and smaller bone-age delay, however, resulted in a shorter interval between M2 and menarche. Several studies have shown that normal-statured AGA girls with an older age at onset of puberty pass through pubertal stages faster than early maturers (24–27).

It is interesting that in our study group BMI had no influence on the age at onset of puberty, but BMI did influence the progression of puberty and the age of menarche (data not shown). In the normal population, it is seen that overweight children mature earlier than nonoverweight children (28). An explanation for why BMI in our study group had no influence on the age at onset of puberty but only on the age at menarche and progression of puberty might be that our SGA children were lean, with a mean BMI (SDS) significantly lower than zero and that there was only a narrow variation in the BMI (SDS) before puberty. However, it is known that during puberty body composition changes significantly and for that reason might have an effect on the age of menarche and progression of puberty in our study group (29). The reason why BMI has influence on the progression of puberty might be that a higher BMI results in higher serum leptin, estrogens, insulin, and IGF-I levels (29). Leptin is thought to be one of the hormonal factors that signals to the brain at which time the body is ready for sexual maturation and reproduction (30–32). Kiess *et al.* (30, 33) also reported that leptin is not the primary signal involved in the initiation of puberty but might act as a permissive signal allowing puberty to proceed when metabolic resources are sensed to be sufficient. Some studies suggest that insulin and IGF-I also have an effect on the mechanism of puberty (34, 35). For future studies, it will be very interesting to evaluate the influence of leptin, insulin, and IGF-I on the progression of puberty.

For the endpoint of puberty, we used AH instead of genital development stage 5 and breast development stage 5 because we experienced that these pubertal stages were not reliable endpoints of pubertal growth. The duration of onset of puberty until AH in boys and girls was not significantly different between the GH-dosage groups. We couldn't compare the duration of onset of puberty with AH with the Dutch reference data because AH was not defined in the Dutch Growth Study. Also, no published data on duration of puberty until AH in SGA were available. Our study shows that a greater bone age delay at onset of puberty was associated with a longer duration of puberty until AH, as has been reported for other conditions (36, 37).

The pubertal height gain, in our study defined as the AH minus the height at onset of puberty, was not significantly less in children receiving 1 mg GH/m^2·d compared with those receiving 2 mg GH/m^2·d. The 95% CI of the mean difference of the pubertal height gain was, however, rather large for boys and girls, indicating that the GH-dose effect on mean pubertal height gain might differ in larger patient groups. The pubertal height gain was less when children were older or taller at onset of puberty. This has also been reported in normal-statured children born AGA (3, 26). TH had no influence on the pubertal height gain. Children with a smaller bone age delay at onset of puberty had a reduced pubertal height gain, because the duration of puberty was also shorter in these children. A French longitudinal study, using comparable pubertal milestones and AH criteria as we did, reported a mean (SD) pubertal height gain in untreated

short SGA children of 23.9 (6.1) and 19.8 (4.9) cm for boys and girls, respectively (38). This indicates that the pubertal height gain of our GH-treated SGA children was similar or more, being 27.0 (8.4) cm for group A and 31.4 (4.1) cm for group B for boys and 19.0 (7.3) cm for group A and 18.9 (5.7) cm for group B for girls. As our previously published 5-yr data have shown, most of our SGA children had their GH-induced catch-up growth during the first 2 yr (10). After 4 yr of GH treatment, the mean height was within the target range for both GH-dosage groups. For that reason, it is not surprising that as both groups entered puberty after at least 4 yr of GH treatment, children growing within their target range did not further increase their height SDS during puberty. On the other hand, because it has been described that discontinuation of GH might lead to catch-down growth in SGA children, it seems advisable to continue GH treatment unless future research would prove otherwise (39).

In conclusion, age at onset of puberty and menarche and progression of puberty of short children born SGA during long-term, continuous GH treatment are comparable with normal-statured AGA children, regardless of a dose of 1 mg or 2 mg GH/m^2·d. In addition, the duration of puberty and the pubertal height gain were not significantly different between the GH-dosage groups.

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