Puberty and Pubertal Growth in GH-treated SGA Children: Effects of 2 Years of GnRHa Versus No GnRHa

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Context: Most studies on puberty in children born small for gestational age (SGA) report height and age at onset of puberty. GH-treated SGA children with an adult height (AH) expectation below −2.5 SDS at onset of puberty can benefit from an additional 2 years of GnRH analog (GnRHa) treatment. There are no data on puberty and growth after discontinuation of GnRHa treatment in GH-treated SGA children.

Objective: This study aimed to investigate the effects on puberty and pubertal growth of 2 years GnRHa vs no GnRHa in GH-treated SGA children.

Methods: This was a GH trial involving 76 prepubertal short SGA children (36 girls) treated with GH. Thirty-two children received additional GnRHa for 2 years. Pubertal stages were 3-monthly assessed according to Tanner.

Results: Age, bone age, and median height at pubertal onset were lower in girls and boys in the GH/GnRHa group compared with the GH group. In girls and boys treated with GH/GnRHa, pubertal duration after stop of GnRHa treatment was shorter than pubertal duration in those with GH only (40.9 vs 46.7 mo; $P = .044$; 50.8 vs 57.5 months; $P = .006$; respectively). Height gain from onset of puberty until AH, including height gain during 2 years of GnRHa treatment, was 25.4 cm in girls and 33.0 cm in boys, which was 6.6 cm more than girls and boys treated with GH only. AH was similar in children treated with GH/GnRHa compared with those with GH only.

Conclusions: GH-treated SGA children who start puberty with an AH expectation below −2.5 SDS and are treated with 2 years of GnRHa have a shorter pubertal duration after discontinuation of GnRHa compared with pubertal duration in children treated with GH only. Height gain from onset of puberty until AH is, however, more due to adequate growth during 2 years of GnRHa treatment resulting in a similar AH as children treated with GH only. (***J Clin Endocrinol Metab*** **101: 0000–0000, 2016)**

Height and age at onset of puberty, as well as the magnitude and duration of pubertal growth are important determinants of adult height, explaining 15–20% of adult height (1). Most studies on puberty in children born small for gestational age (SGA) report height and age at onset of puberty but not pubertal duration. Study results are difficult to compare due to the use of various definitions for the milestones of puberty, but most authors seem to agree that puberty in short SGA children starts within the normal range but relatively early for their short stature (2–6).

In children born SGA with persistent short stature, GH is an approved therapy for increasing adult height (7–9). GH-treated SGA children with an expected adult height (AH) <–2.5 SDS at onset of puberty benefit from additional treat-

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Abbreviations: AH, adult height; BA, bone age; BMI, body mass index; GnRHa, GnRH analog; M2, Tanner stage II breast development; SGA, small for gestational age.

ment with a GnRH analog (GnRHa) for 2 years from onset of puberty to increase AH (10). There are, however, no data on puberty and pubertal growth after discontinuation of GnRHa treatment in GH-treated SGA children.

Based on our clinical experience, we expected that GH-treated SGA children treated with an additional 2 years of GnRHa from onset of puberty would show an accelerated pubertal progression after discontinuation of GnRHa resulting in less pubertal growth than children treated with GH only. However, due to the additional height gain during postponement of puberty by 2 years of GnRHa treatment, we expected AH and AH SDS to be similar in children treated with combined GH/GnRHa compared with those treated with GH only.

Subjects and Methods

In the Dutch SGA study, children could start GH treatment from the age of 8 years, either being prepubertal or in early puberty. The present study group consisted of 76 short SGA children (36 girls), a subgroup of the total Dutch SGA study, who were prepubertal at start of GH treatment and were followed until AH. Body composition, glucose homeostasis, blood pressure, lipid levels, and AH have been reported for the total Dutch SGA study (10–12). Pubertal development in the present study group has never been published. Children were included when they met the following criteria: 1) birth length and/or birth weight SDS for gestational age less than −2.0 (13); 2) current height less than –2.5 SDS; 3) prepubertal stage at start of GH treatment (Tanner stage I); 4) well-documented growth data from birth to start of treatment; and 5) normal karyotype in all girls. None of the children were GH deficient according to normal serum IGF-I levels (IGF-I level >−2 SDS) and stimulation tests (GH peak >7.7 ng/mL) or overnight GH profiles.

Children started with daily sc somatropin treatment when prepubertal and were treated until AH. A height of less than 140 cm at onset of puberty was used to identify children with an AH expectation of less than −2.5 SDS, based on Dutch reference values (14, 15). These children received 2 years of GnRHa treatment (leuprolide acetate depots, 3.75 mg sc every 4 wk) from onset of puberty in addition to GH treatment (GH/GnRHa group). During GnRHa treatment, puberty was sufficiently suppressed in all children, both clinically and by GnRHa-stimulating tests or overnight-gonadotropin profiles (16, 17). Children who started puberty with a height above 140 cm were treated with GH only (GH group). Children were treated with GH 1 mg/m^2/d (~0.033 mg/kg/d) until onset of puberty. At onset of puberty, they were randomly assigned to treatment with either GH 1 or 2 mg/m^2/d after stratification for sex, pubertal stage, and parental height (one or two parents with a height <−2 SDS vs both parents with a height >–2 SDS). Every 3 months, the GH dose was adjusted to calculated body surface area. Figure 1 shows the treatment regimen during the study. Seventy-one children reached AH (defined as height reached when growth velocity had decreased to <0.5 cm during the last 6 months, and bone age [BA] was ≥15 y in girls and ≥17 y in boys), or near AH (defined as height velocity between 0.5 and 2 cm during the last 6 mo and adult pubertal stage). Five children did not reach adult height; one boy was still growing and four children dropped out for the following reasons: lack of motivation despite ongoing catch-up growth (n = 2), social problems (n = 1), emigration (n = 1). Data of these five children were used until the highest pubertal stage attainment during the study.

The study was performed according to the Helsinki Declaration and approved by the medical ethics committees of the participating centers. Written informed consent was obtained from parents or guardians of each child and from children who were 12 years or older. Due to ethical considerations, the medical ethics committees did not allow a randomized untreated short-SGA group.

Measurements

Height and weight were determined at start and every 3 months by the same physicians. Height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Holtain, Ltd.). Weight was measured to the nearest 0.1 kg on a digital scale (Servo Balance KA-20-150S, Servo Berkel Prior). Body mass index (BMI) was calculated (kilograms per square meter, rounded to the nearest tenth). Height, weight, and BMI were transformed into SDS for sex and chronological age according to Dutch references (14), using Growth Analyzer Research Calcu-

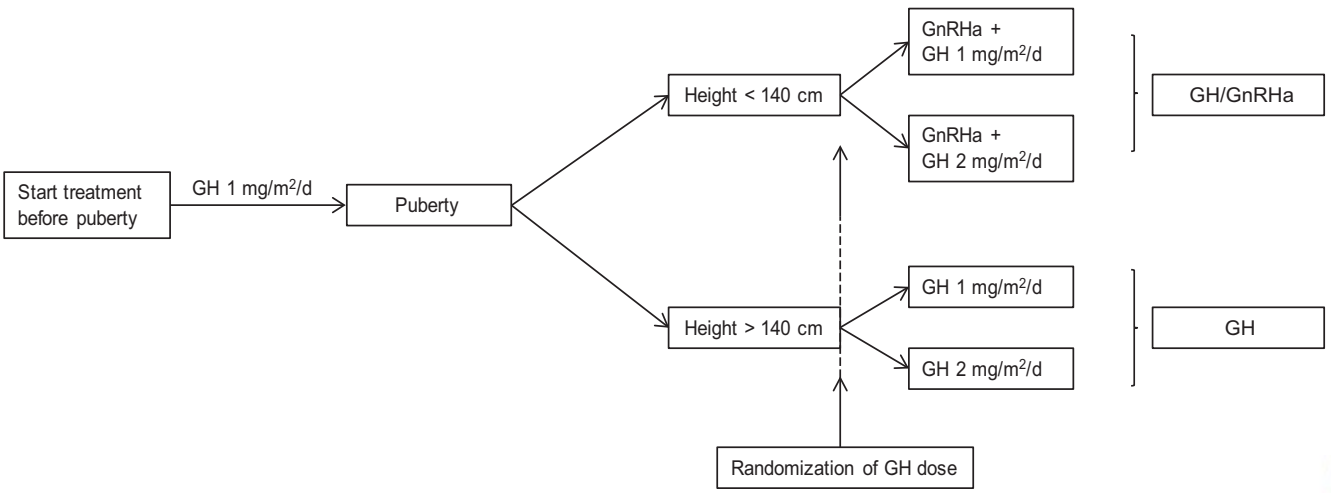

Figure 1. Flowchart of treatment regimen of prepubertal children of the Dutch SGA study.

lation Tools (https://growthanalyser.org). Radiographs of the left hand and wrist were taken annually. BA was determined at start of GH treatment and yearly thereafter by one investigator (M.v.d.S.) according to Greulich and Pyle (18).

Pubertal development

Pubertal stages were assessed according to the method of Tanner and Whitehouse (19) at each 3-monthly visit, allowing quite precise determination of pubertal onset, which was defined as breast development stage II for girls according to Tanner (19) and a testicular volume equal or more than 4 mL for boys as determined by means of a Prader orchidometer. End of GnRHa treatment, and thus restart of puberty, was defined as 4 weeks after the last GnRHa injection. At each 3-monthly visit, girls were asked whether and when they had their menarche.

We defined several periods during pubertal development to compare pubertal duration between children treated with GH/GnRHa and those treated with GH only. In girls, Period 1 was defined as the period between onset of puberty (M2) and menarche. In boys, Period 1 was defined as the period between onset of puberty (a testicular volume of 4 mL) and a testicular volume of 16 mL. Because we wanted to be certain that there was central puberty, we performed a GnRH analog test after the appearance of the first clinical signs (M2 in girls and a testicular volume of 4 mL in boys). This resulted in a delay between onset of puberty and start of GH/GnRHa treatment during which pubertal development progressed. Period 1 in girls and boys treated with GH/GnRHa was therefore divided in two separate periods; onset of puberty until start of GnRHa treatment (period 1A) and restart of puberty after stop of GnRHa until menarche in girls or until a testicular volume of 16 ml in boys (period 1B). In girls, Period 2 was defined as the period between menarche and AH. In boys, Period 2 was defined as the period between a testicular volume of 16 mL and AH.

Statistical analyses

We used the same definitions for pubertal milestones as the Fourth Dutch National Growth Study (1997), which served as reference for age and height at onset of puberty and age at menarche of normal-statured children born appropriate for gestational age (controls) (14). Statistical analyses were performed with SPSS version 21. Distribution of variables was determined by Kolmogorov-Smirnov test and normal Q-Q-plots. Data are expressed as median (interquartile range). Differences between the groups were calculated using Mann-Whitney *U* test. $P < .05$ were considered statistically significant.

Results

Onset of puberty

Table 1 lists the clinical data of all 76 prepubertal children compared with Dutch references. All children started GH treatment 1 mg/m^2/d when prepubertal. Median GH treatment duration until onset of puberty was 2.1 years (1.0–2.8 y) in girls and 2.7 years (1.6–3.9 y) in boys.

Girls in the GH/GnRHa group started puberty at a similar age compared with Dutch references, whereas girls in the GH group started puberty significantly older compared with references. Age and BA at pubertal onset were significantly younger in girls in the GH/GnRHa group compared with girls in the GH group. As expected, median height in centimeters at pubertal onset was significantly lower in girls in the GH/GnRHa group (134.6 cm) than in the GH group (143.1 cm; $P < .001$), but their height SDS at onset of puberty was similar. BMI SDS at pubertal onset was similar between groups.

Boys in the GH/GnRHa group started puberty at a similar age compared with Dutch references, whereas boys in the GH group started puberty significantly older compared with references. Age and BA at pubertal onset were significantly younger in boys in the GH/GnRHa group compared with boys in the GH group. As expected, median height in centimeters at pubertal onset was significantly lower in boys in the GH/GnRHa group (137.0 cm) than in the GH group (143.4 cm; $P < .001$), but their height SDS at onset of puberty was similar. BMI SDS at pubertal onset was similar between groups.

Bone maturation

At onset of puberty, BA was significantly younger in girls and boys treated with GH/GnRHa than those treated with GH only (Table 1). BA at onset of puberty was similar in children who were randomly assigned to receive either 1 or 2 mg/m^2/d. In the GH/GnRHa group, the ratio ΔBA/ΔCA during 1 year of GnRHa treatment with sufficient suppression of puberty was 0.3 years in girls and 0.5 years in boys. In the GH group, the ratio ΔBA/ΔCA during 1 year after onset of puberty was 1.0 year in girls and 0.75 years in boys. For girls, the ratio ΔBA/ΔCA was significantly lower in the GH/GnRHa group compared with the GH group ($P = .003$), whereas in boys the ratio ΔBA/ΔCA was not significantly different ($P = .119$).

Pubertal duration

Because we wanted to be certain that there was central puberty, we performed a GnRH-analog test after the appearance of the first clinical signs of puberty (M2 in girls and a testicular volume of 4 mL in boys). In girls and boys treated with GH/GnRHa, this resulted in a delay between onset of puberty and start of GnRHa treatment during which pubertal development progressed. The median delay was 3.4 months (1.6–4.8 mo) in girls and 3.6 months (1.5–5.0 mo) in boys. During these months, puberty progressed and for that reason this period (1A) was added to the pubertal duration after stop of GnRHa treatment (1B) (see Figure 2, A and B; period 1 [A + B]).

Figure 2A shows the pubertal duration in girls. In girls treated with GH/GnRHa, period 1A + 1B lasted 21.3 months (15.0–26.2 mo), which was not significantly dif-

Table 1. Clinical Characteristics of 76 Prepubertal GH-treated SGA Children Versus Dutch References

Characteristic	GH/GnRHa	GH	*P* Value[b]	GH/GnRHa	Dutch References[c]
Start of GH					
Girls					
Age , y	10.1 (6.9 to 11.1)	9.9 (9.7 to 10.7)	.837		
Height, cm	123.4 (109.0 to 128.0)	124.9 (120.1 to 127.1)	.334		
Height, SDS	−3.0 (−3.4 to −2.9)	−3.0 (−3.5 to −2.7)	.219		
Boys					
Age, y	9.0 (6.7 to 11.0)	10.1 (9.1 to 11.3)	.065		
Height, cm	116.0 (108.5 to 128.6)	122.9 (117.4 to 131.2)	**.039**		
Height, SDS	−3.3 (−3.7 to −2.7)	−2.9 (−3.2 to −2.6)	.151		
Onset of puberty				Restart Puberty	
Girls	19	17		19	2266
GH dose, 1/2 mg/m^2/d	8/11	10/7	.317	8/11	
Age, y	11.5 (10.3 to 12.0)	12.4 (12.0 to 12.8)[a]	**.001**	13.9 (12.8 to 14.5)	10.7
BA, y	10.8 (10.5 to 11.0)	11.3 (11.0 to 12.0)	**.003**	12.0 (11.5 to 12.3)	
BA delay, y	−0.8 (−1.3 to 0.1)	−0.8 (−1.7 to −0.6)	.248	−1.6 (−2.5 to −1.0)	
Height, cm	134.6 (130.3 to 136.1)	143.1 (140.3 to 145.5)	**<.001**	148.9 (144.4 to 153.8)	
Height, SDS	−2.6 (−3.0 to −1.9)	−2.1 (−2.8 to −1.7)	.257		
BMI, SDS	−0.6 (−1.3 to −0.3)	−1.0 (−1.6 to −0.3)	.496	−0.6 (−1.0 to 0.1)	
Boys	13	27		12	2524
GH dose, 1/2 mg/m^2/d	8/5	12/15	.311	7/5	
Age, y	11.4 (10.9 to 12.8)	13.0 (12.6 to 13.5)[a]	**<.001**	13.6 (13.2 to 14.8)	11.5
BA, y	10.5 (10.0 to 11.4)	12.3 (11.4 to 12.8)	**.001**	12.6 (12.3 to 13.4)	
BA delay, y	−0.7 (−2.4 to 0.03)	−1.0 (−1.3 to −0.2)	.919	−1.1 (−1.7 to −0.4)	
Height, cm	137.0 (134.7 to 138.2)	143.4 (141.2 to 146.7)	**<.001**	152.2 (149.5 to 153.3)	
Height, SDS	−2.2 (−2.8 to −1.7)	−2.2 (−2.5 to −1.7)	.955		
BMI, SDS	−1.3 (−2.1 to −0.2)	−0.8 (−1.7 to −0.3)	.718	−1.0 (−2.3 to −0.1)	

Data are expressed as median (IQR) unless written otherwise. Bold values indicate a statistically significant difference.

[a] $P < .001$ compared with Dutch references.

[b] *P*-value: comparison between GH/GnRHa and GH group.

[c] Data of Fourth Dutch National Growth study (14).

ferent from period 1 in girls treated with GH only, which lasted 17.8 months (10.4–27.6 mo) ($P = .466$). Period 2, menarche until AH, was 21.6 months (16.3–29.0 mo) in girls treated with GH/GnRHa, which was shorter than the 27.8 months (20.3–31.8 mo) in those treated with GH only ($P = .047$). Time from onset of puberty until AH, period 1 (A and B) + 2, was 40.9 months (33.7–48.5 mo) in girls treated with GH/GnRHa, which was shorter than the 46.7 months (41.1–58.6 mo) in girls treated with GH only ($P = .044$). Median age at menarche was significantly older in girls treated with GH/GnRHa compared with those treated with GH only (14.6 vs 14.0 y; $P = .001$). Girls in both groups had their menarche at an older age compared with the median age of 13.15 years in healthy Dutch references ($P < .001$ and $P = .004$, respectively). There was no significant difference in pubertal duration between the two GH dose groups.

Figure 2B shows the pubertal duration in boys. In boys treated with GH/GnRHa, period 1A + 1B until a testicular volume of 16 mL, lasted 24.4 months (16.7–29.2 mo) which was not significantly different from period 1 in boys treated with GH only which lasted 27.1 months (21.6–39.8 mo) ($P = .111$). Period 2, from a testicular volume of 16 mL to AH, was 23.9 months (19.3–33.9 mo) in boys treated with GH/GnRHa and 27.3 months (21.3–33.1 mo) in those treated with GH only ($P = .887$). Time from onset of puberty until AH, period 1(A and B) + 2, was 50.8 months (47.4–53.6 mo) in boys treated with GH/GnRHa, which was shorter than the 57.5 months (50.9–62.1 mo) in boys treated with GH only ($P = .006$). There was no significant difference in pubertal duration between the two GH dose groups.

Growth from onset of puberty to AH

Figure 3A shows the growth from onset of puberty to AH in girls. At onset of puberty, the median height of girls in the GH/GnRHa group was 134.6 cm (130.3–136.1 cm), which was significantly lower than the median height of girls in the GH group, which was 143.1 cm (140.3–145.5 cm) ($P < .001$). During 2 years of GnRHa treatment, the median height gain in girls was 12.7 cm (11.1–13.7 cm). At restart of puberty, 4 weeks after discontinuation of GnRHa treatment, median height was 148.9 cm (144.4–153.8 cm) in girls treated with GH/GnRHa and their median height gain during period 1A + 1B until menarche was 9.0 cm (7.9–11.1 cm), which was not significantly

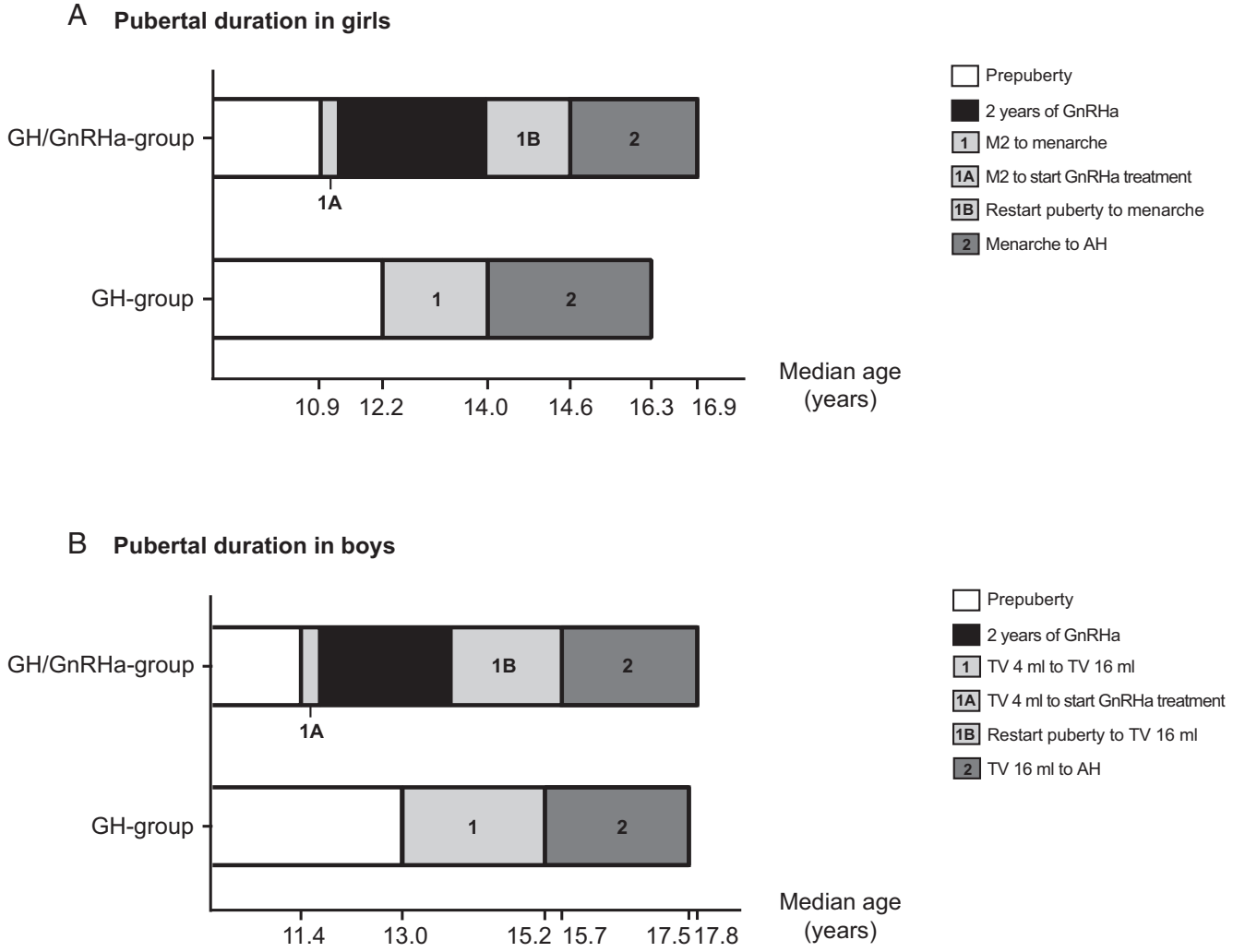

Figure 2. A, Pubertal duration in girls. B, Pubertal duration in boys. TV, testicular volume.

different from the median height gain of 9.7 cm (7.2–17.6 cm) in period 1 in girls treated with GH only ($P = .398$). Median height gain in period 2 from menarche until AH was 3.9 cm (3.2–4.4) in girls treated with GH/GnRHa, which was significantly less than the 5.6-cm (4.4–8.5 cm) gain in girls in the GH group ($P = .002$). Median height gain during period 1(A + B) + 2 until AH was 13.3 cm (11.1–14.3 cm) in girls treated with GH/GnRHa and 18.8 cm (13.8–23.6 cm) in girls treated with GH only ($P = .003$). The median total height gain from onset of puberty until AH, including the height gain during GnRHa treatment, was 25.4 cm (24.4–26.4 cm) in girls treated with GH/GnRHa, which was 6.6 cm more than in girls treated with GH only who gained 18.8 cm (13.8–23.6 cm) ($P = .001$). Girls with GH/GnRHa treatment were shorter at pubertal onset than those treated with GH only but they reached a similar median AH (160.4 vs 162.7 cm; $P = .217$) and AH SDS (−1.6 vs −1.2; $P = .217$). In girls treated with GH/GnRHa and those treated with GH only, there was no significant difference in pubertal growth between the two GH dose groups.

Figure 3B shows the growth from onset of puberty to AH in boys. At onset of puberty, the median height of boys in the GH/GnRHa group was 137.0 cm (134.7–138.2 cm), which was significantly lower than the median height of boys in the GH group, which was 143.4 cm (141.2–146.7 cm) ($P < .001$). During 2 years of GnRHa treatment, the median height gain in boys was 13.1 cm (11.1–14.4 cm). At restart of puberty, 4 weeks after discontinuation of GnRHa treatment, median height was 152.2 cm (149.5–153.3 cm) in boys treated with GH/GnRHa and their median height gain during period 1A + 1B until a testicular volume of 16 mL was 13.5 cm (11.1–17.7 cm), which was significantly less than the median height gain in period 1 in boys treated with GH only who gained 18.8 cm (16.5–21.8 cm) ($P = .020$). Median height gain in period 2 from a testicular volume of 16 mL until AH was 6.1 cm (2.8–7.9 cm) in boys treated with GH/GnRHa, which was not sig-

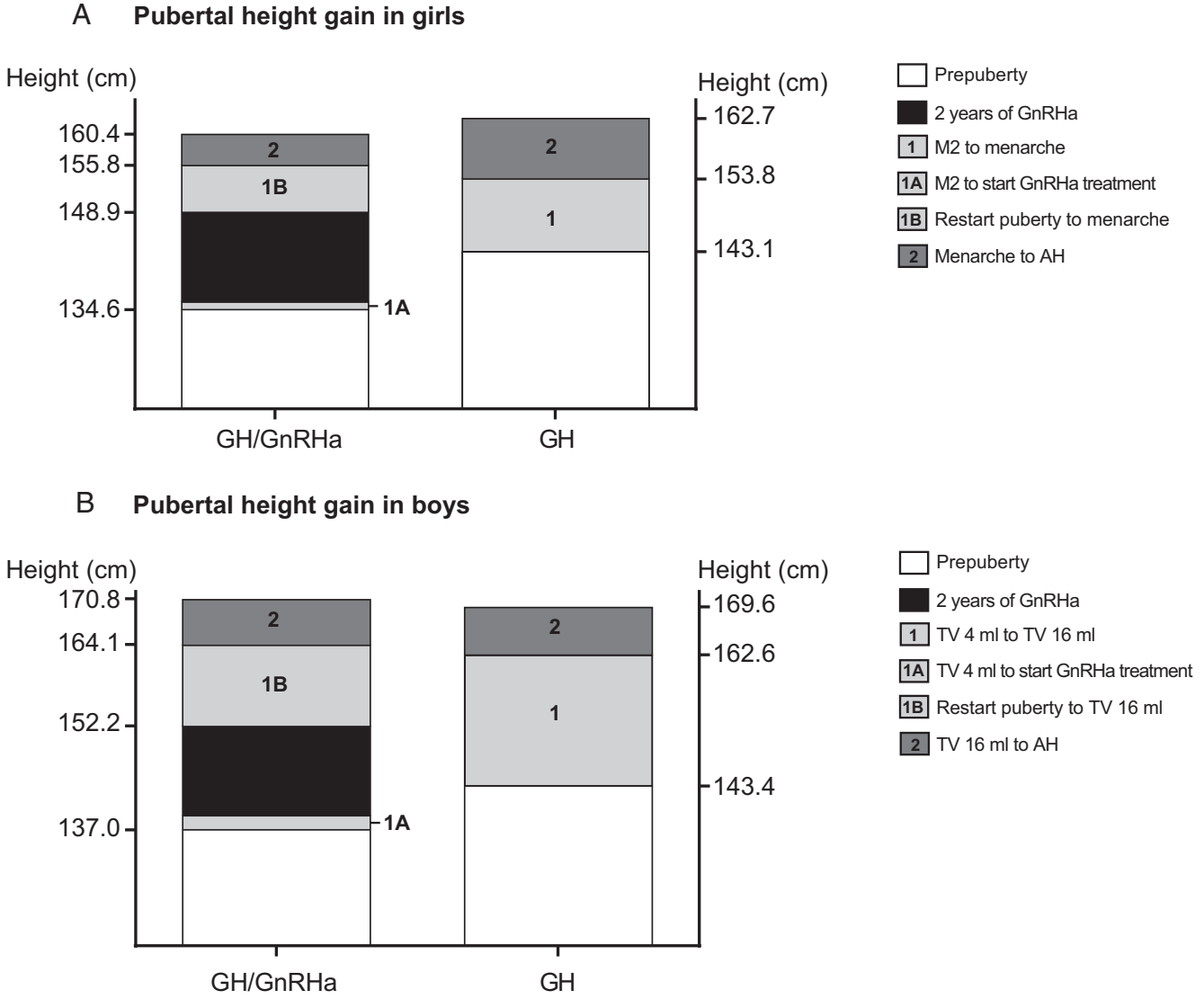

Figure 3. A, Pubertal height gain in girls. B,Pubertal height gain in boys. TV, testicular volume.

nificantly different from the median height gain of 7.7 cm (4.0–9.4 cm) in period 2 in boys treated with GH only (P = .354). Median height gain during period 1(A + B) + 2 until AH, was 21.0 cm (19.4–22.9 cm) in boys treated with GH/GnRHa and 26.4 cm (22.6–29.6 cm) in boys treated with GH only (P = .001). The median total height gain from onset of puberty until AH, including the height gain during GnRHa treatment, was 33.0 cm (29.9–37.4 cm) in boys treated with GH/GnRHa, which was 6.6 cm more than in boys treated with GH only who gained 26.4 cm (22.6–29.6 cm) (P = .001). Boys with GH/GnRHa treatment were shorter at pubertal onset than those treated with GH only but they reached a similar median AH (170.8 vs 169.6 cm; P = .884) and AH SDS (−1.9 vs −2.0; P = .960). In boys treated with GH/GnRHa and those treated with GH only, there was no significant difference in pubertal growth between the two GH dose groups.

Discussion

This study presents the long-term effects of 2 years of additional GnRHa treatment on puberty and pubertal growth in GH-treated children born SGA with an AH expectation below −2.5 SDS at onset of puberty. Although children treated with combined GH/GnRHa were shorter at onset of puberty and had a shorter pubertal duration after discontinuation of GnRHa, their total height gain from onset of puberty until AH was greater compared with those treated with GH only due to an adequate growth during 2 years of GnRHa. This resulted in a similar AH as those treated with GH only.

When the option of additional GnRHa treatment is discussed with parents, they often have questions on how much height their child will gain during GnRHa treatment and what to expect after discontinuation of GnRHa treatment; when to expect menarche and how much height gain

will occur after menarche. Data to answer these questions were lacking. Our study presents data on puberty and pubertal growth when 2 years of GnRHa treatment is added to GH treatment in SGA children with an AH expectation below −2.5 SDS at onset of puberty. We show that girls and boys grew approximately 13 cm during 2 years of GnRHa treatment. Girls treated with 2 years of additional GnRHa had their menarche approximately 1.5 years after restart of puberty, with a range from 1–2 years, which is in line with findings in girls with central precocious puberty treated with GnRHa (20–22). They grew nearly 10 cm from restart of puberty until AH and reached their AH approximately 3 years after restart of puberty. From menarche until AH, girls treated with GH/GnRHa grew approximately 4 cm compared with nearly 5.5 cm in girls treated with GH only. Boys grew approximately 20 cm from restart of puberty until AH and reached their AH nearly 4 years after restart of puberty. Total growth from onset of puberty until AH was 6.6 cm more in girls and boys treated with GH/GnRHa than in those treated with GH only, which resulted in a similar AH in those treated with GH/GnRHa and GH only. In children treated with GH/GnRHa, total duration from onset of puberty until AH was longer because of the additional GnRHa treatment, which delayed puberty for 2 years. Without the 2 years of GnRHa treatment, pubertal duration was, however, shorter compared with children treated with GH only. The shorter pubertal duration after GnRHa treatment was not due to more progression in bone maturation according to Greulich and Pyle (18), as BA at onset of puberty was significantly younger and BA development during GnRHa treatment was slower in the GH/GnRHa group compared with the GH group.

A possible explanation for the shorter pubertal duration after GnRHa treatment in children treated with GH/GnRHa could be continuing senescence of the growth plate, the progressive loss of function and structural involution of the growth plate, which is growth dependent (23), during GnRHa treatment. When growth plates are more senescent, and have expended more of their growth potential, a shorter exposure to estrogen is sufficient to complete growth plate fusion (24). There are no other studies reporting pubertal duration after discontinuation of GnRHa treatment in SGA children and therefore comparing our results to other studies was not possible.

Adult height in GH-treated children is influenced by pubertal timing and early onset can result in a loss of prepubertal gain in height SDS. Although our study was not designed to evaluate onset of puberty, our findings show that the total group of GH-treated children born SGA did not start puberty at a younger age compared with normal-statured Dutch children born appropriate for gestational age. Children in the GH/GnRHa group started puberty at a similar age as Dutch references, but relatively early for their actual height which is in line with previous studies (2–6). Age at onset of puberty and at menarche was significantly older in the GH group, although within the normal age range for Dutch references (14), which is in line with previous studies in SGA children (25–27). Given that pubertal development in the GH/GnRHa group was delayed for 2 years by additional GnRHa treatment, comparing age at menarche in the GH/GnRHa group to Dutch references would be inappropriate.

This present study was not designed to investigate pubertal postponement by GnRHa vs no postponement in a randomized design. GnRHa treatment in addition to GH depended on absolute height at start of puberty and adult height prediction. Despite this limitation, our study provides pragmatic data on expectations for GH-treated children born SGA in whom additional GnRHa treatment is contemplated and shows a beneficial effect of GnRHa treatment on height which is consisted with previous studies in other populations (28–30).

GnRHa treatment was well tolerated in all children and no adverse effects were reported. Metabolic health, insulin sensitivity, and β-cell function at AH showed similar results in children treated with combined GH/GnRHa and those treated with GH only (11, 12). In the current study, all girls treated with GnRHa reported regular cycles at AH and one pregnancy after AH with normal offspring was reported. Long-term followup in girls with central precocious puberty treated with GnRHa also showed that the interruption of the GnRH axis in childhood did not impair reproductive function in adulthood (21). Definitive conclusions on long-term reproductive function in young women born SGA treated with GnRHa can, however, not be made because long-term followup data are not yet available.

In conclusion, when GH-treated SGA children with an AH expectation below –2.5 SDS at onset of puberty are treated with 2 years of additional GnRHa treatment, their pubertal duration after discontinuation of GnRHa treatment is shorter compared with the pubertal duration in children with an AH expectation above −2.5 SDS treated with GH only. Although they are shorter at onset of puberty, adequate growth during 2 years of GnRHa treatment leads to a better total growth from onset of puberty until AH resulting in a similar AH as those treated with GH only.

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