Regulation and modulation of growth : insights from human and animal studies

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Chapter 3

Final height outcome following 3 years of growth hormone and gonadotropin releasing hormone agonist treatment in short adolescents with relatively early puberty

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Abstract

Objective: To assess final height (FH) and adverse effects of combined growth hormone (GH) and gonadotropin releasing hormone agonist (GnRHa) treatment in short adolescents born small for gestational age or with normal birth size (idiopathic short stature, ISS).

Design and patients: 32 adolescents with Tanner stage 2-3, age and bone age (BA) <12 (girls) or <13 (boys) years, height SDS<–2.0 SDS or between –1.0 and –2.0 SDS plus a predicted adult height (PAH_0) <–2.0 SDS, were randomly allocated to receive GH+GnRHa (n=17) or no treatment (n=15) for 3 years. FH was assessed at the age of ≥18 (girls) or ≥19 years (boys).

Results: FH was not different between treatment and control groups. Treated children had a higher height gain (FH–PAH_0) than controls: 4.4 (4.9) and –0.5 (6.4) cm, respectively ($p<0.05$). FH was higher than PAH_0 in 76% and 60% of treated and control subjects, respectively. During follow-up, 50% of the predicted height gain at treatment withdrawal was lost, resulting in a mean gain of 4.9 cm (range –4.0 to 12.3 cm) compared to controls. Treatment did not affect body mass index (BMI) or hip bone mineral density (BMD). Mean lumbar spine BMD and bone mineral apparent density (BMAD) tended to be lower in treated boys, albeit statistically not significant.

Conclusion: Given the expensive and intensive treatment regimen, its modest height gain results and the possible adverse effect on peak bone mineralization in males, GH+GnRHa can not be considered routine treatment for children with ISS or SGA.

Introduction

Short children with a relatively early onset of puberty often attain a poor final height (FH), due to premature growth acceleration and epiphyseal fusion induced by the pubertal rise in sex steroid levels (1). Growth hormone (GH) treatment increases FH in children with idiopathic short stature (ISS) or a persistent short stature after being born small for gestational age (SGA), particularly when initiated in early childhood (2). The effect of GH therapy is dose-dependent, with lower dosages being less efficacious (3;4), whereas too high doses may accelerate growth velocity and stimulate a rapid progression through puberty, possibly limiting FH gain (5). Once puberty has started, GH treatment may limit FH gain, because by that time the process of epiphyseal maturation has already been set in motion (6).

An alternative for GH treatment is to delay or halt pubertal onset with gonadotropin releasing hormone agonists (GnRHa). However, in many children, GnRHa therapy concomitantly decreases growth velocity to values below the normal prepubertal pace, which may at least in part result from accelerated growth plate senescence induced by prior estrogen exposure (7).

Combined GH and GnRHa treatment in adolescents with short stature has been analyzed in a few studies with limited numbers of patients and conflicting results. None of these were randomized controlled trials (RCT) and final height results are scarce. Height gain defined as the difference between FH and baseline height prediction (PAH_0) was 1.0-10.0 cm (8-13). Treatment response was usually analyzed by comparison with a GH-treated group (12;14), or a not randomly assigned, untreated control group (9;9;15) or no control group at all (8). Moreover, most of the trials focused on girls only and excluded children with a persistent short stature after being born SGA.

In 2001, we reported three years' results of the first RCT investigating GH+GnRHa treatment in short, early pubertal adolescents with ISS or SGA. We concluded that three years of GnRHa treatment was effective in suppressing puberty, while growth velocity was preserved due to addition of GH, resulting in a significant gain in PAH without demonstrable side effects (16). Assessment of the motives of adolescents and their parents to participate in this trial and psychosocial functioning of the participants during treatment were described recently (17;18). Psychosocial functioning in young adulthood will be described elsewhere (Visser-van Balen, submitted for publication). Here we report FH data and analyze possible adverse effects of treatment on bone mineral (apparent) density (BM(A)D) and body mass index (BMI).

Material and methods

Patients

This report includes FH results from 32 out of 40 adolescents with short stature that originally enrolled in a multicenter study in the Netherlands in 1993-96. Inclusion criteria were: chronological age (CA) and bone age (BA) <12 (girls) or <13 years (boys); pubertal stage of G2-3 (boys) or B2-3 (girls); height at baseline H_0<–2.0 SDS for Dutch references (19) or between –1.0 and –2.0 SDS with PAH_0 <–2.0 SDS (according to Bailey & Pinneau, (20)); maximum serum GH level >10 µg/l (1 mg = 2IU, using The first International Reference Population of hGH, MRC London, code 66/217 as standard) after provocation (exercise, arginine, clonidine, L-dopa, or glucagon), and a normal sitting height/subischial leg length ratio (between P3 and P97 (21)). Screening blood tests and urinalysis were normal. No organic cause of growth failure, primary bone disease, chronic illness, or dysmorphic syndrome were present. During the trial phase, fasting glucose and insulin levels remained within the normal range in all children. Markers for bone formation (osteocalcin, alkaline phosphatase, PICP and PIIINP) were not different between treatment and control groups. Details of the subjects and data obtained after withdrawal of treatment were reported previously (16).
The protocol was approved by medical ethical review boards at the four participating centers (Amsterdam, Utrecht, Eindhoven, Rotterdam). Before conducting any study-related procedure, written informed consent was obtained from parents, and, when appropriate, also from the participants. This clinical trial was registered in the *meta*Register of Controlled Trials (ISRCTN82161629) of the Current Controlled Trials Ltd.

Study design

Forty patients were randomly allocated to receive combined treatment with GH+GnRHa or no treatment for a period of three years (see fig.1). GH (Genotropin®, Pharmacia, Sweden; now Pfizer, New York, USA) was given in a dose of 1.33 mg (4 IU)/m^2/day subcutaneously, equivalent to 0.05 mg/kg body weight/day. A 3.75 mg 1-month depot preparation of GnRHa was intramuscularly administered (Triptorelin (Decapeptyl®) Ferring, Malmö, Sweden; after withdrawal by Ferring in 1998, triptorelin from Ipsen, Paris, France was used). This corresponded with a mean Triptorelin dose of 125 µg/kg at start of treatment and 67 µg/kg at discontinuation of treatment.

Randomization was performed separately in children born SGA, defined as birth length <–2.0 SDS (22). Directly after randomization, 4 patients (two from each group) refused to start the intervention they were randomly allocated to receive and dropped out. Additionally, 2 patients dropped out from the control group due to a lack of motivation for visiting the outpatient clinic during the trial phase and another 2 (one in each group) could not be traced and were lost to follow-up.
Adolescents were considered to have attained final height if treatment withdrawal was at least 3 years prior to evaluation and chronological age was greater than or equal to 18 (girls) or 19 years (boys). FH, being the average of four measurements made by a single observer using a Harpenden stadiometer, was determined at an outpatient clinic visit or at a house visit.

Bone mineral density

BMD of the lumbar vertebrae and hip were measured by dual-energy X-ray absorptiometry (DXA) at the moment of FH analysis. DXA-scans were performed at the Department of Radiology of the VU University Medical Center in Amsterdam or at the Diagnostic Center Eindhoven using a Hologic Delphi 4500A or a Hologic Delphi W-type 70991 (Hologic, Waltham, MA, USA), respectively. Cross-calibration with phantoms demonstrated that the DXA machines were comparable, and data from both centers were pooled. Each machine was calibrated using the manufacturer's 'daily quality control' protocol. Z-scores were calculated, using hip reference values based on the National Health and Nutrition Examination Survey from 1988-1991 (NHANES) (23) and Hologic reference values for lumbar spine (L1-L4). To correct for bone size, DXA-derived data were used to calculate lumbar spine BMAD (24). BMAD Z-scores could not be calculated due to the lack of appropriate reference values.

Outcome parameters

Four outcome parameters were used to evaluate response to treatment: 1) FH (SDS); 2) FH minus baseline height (H_0) (SDS); 3) FH minus PAH_0 according to Bayley and Pinneau (20) (cm); and 4) FH minus target height (TH; cm). FH minus PAH_3 (PAH at discontinuation of treatment) was also calculated, to show the difference between final outcome and height prediction at discontinuation of treatment. All SD scores were based on Dutch references (19). For calculation of FH SDS, the age of each patient was set at 21 years, enabling comparison of FH with height distribution in the normal adult population. For 3 patients, a bone age radiograph at baseline

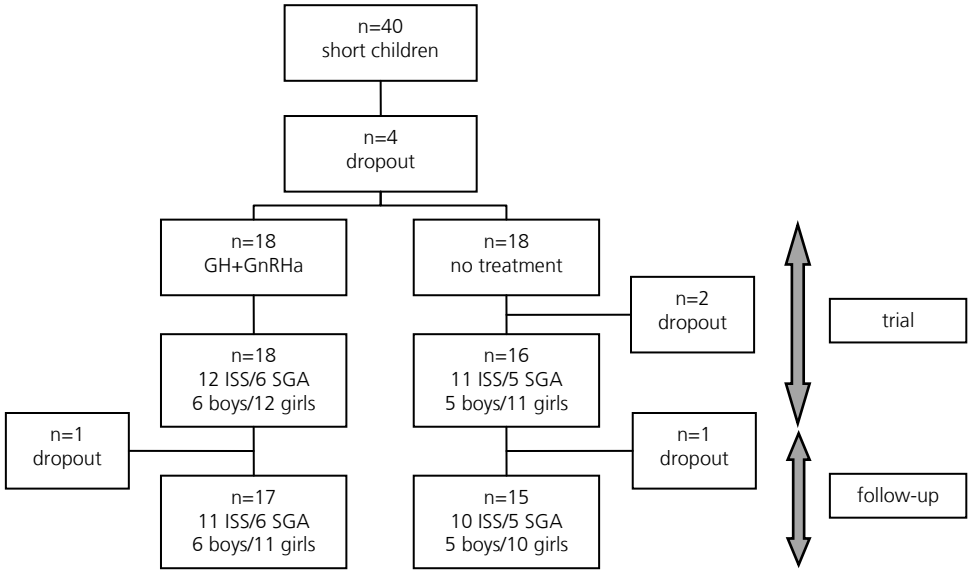
was not available, and BA determination closest to this time point was used and transformed to $BA_{baseline}$ as follows: $BA_{baseline}$ = (BA_{visit}/ Chronological age visit) x $Age_{baseline}$.

TH was calculated as midparental height plus or minus 6 cm (for boys and girls, respectively), plus 3 cm to correct for the average secular trend in the Netherlands (25). One patient's TH could not be calculated, because of adoption from a foreign country and absence of height data of his biological parents.

The following outcome parameters were used to analyze possible effects of GH+GnRHa treatment on bone mineralization and body weight: 1) Lumbar spine BMD (SDS) and BMAD (g/cm^3); 2) Hip BMD (SDS); and 3) BMI (SDS).

Figure 1

Trial design.



Statistical analysis

The study was designed to compare the effects of GH+GnRHa treatment with those of no treatment on final height. Statistical analyses were performed using the statistical package SPSS, version 11.0.1 (26). Results are expressed as mean and SD. Comparisons among treatment and control groups were made using Student's unpaired *t*-tests. Possible interactions between GH+GnRHa treatment and the baseline predictors gender, diagnostic subgroup, age at baseline (age_0), height at baseline (H_0SDS), and bone age delay (CA–BA) were analyzed by means of linear regression analysis using ANOVA. The significance level was set at 0.05.

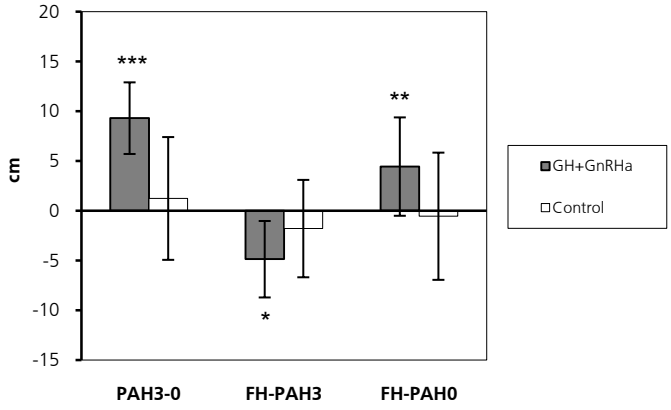
Results

A complete case analysis was carried out for the remaining 32 out of 40 originally included patients (80%). One patient from the GH+GnRHa group discontinued treatment after 2 years due to a lack of motivation, but her near-final height two years after termination of treatment was included in the evaluation. Anthropometric data were not statistically different between treatment and control groups at baseline, but predicted adult height and target height happened to be about 3 cm lower in the treatment group. During the trial phase, clinical (Tanner stage) and biochemical (serum estradiol and testosterone levels) evaluation demonstrated that pubertal development was effectively arrested in the GH+GnRHa group, while puberty progressed in the control group (16). After withdrawal of therapy, pubertal development immediately resumed, with most children from the GH+GnRHa group reaching Tanner V development within 1-2 years and most girls reaching menarche within 1 year. All participants were sexually mature at final analysis.

There was a significant gain in PAH of 9.3 cm after three years of GH+GnRHa treatment, compared with 1.2 cm gain in the control group (fig. 2a). There was no significantly different pattern between the two diagnostic subgroups and genders in changes in height parameters.

Figure 2

Height gain compared with predicted adult height at baseline (FH-PAH_0) and after discontinuation of treatment (FH-PAH_3); in cm. *p<0.1; **p<0.05; ***p<0.001.



Effect on growth

Patient characteristics at start, after treatment discontinuation, and at the moment of FH analysis are listed in table 1. FH data were collected at a mean age of 19.9 (1.8) and 20.9 (1.0) years in girls and boys, respectively. The mean treatment period was 3.0 yr (range 2.8-3.3 yr). The mean period elapsed

between treatment discontinuation and final analysis was 5.7 yr (range 3.6-8.7 yr).

FH SDS [–2.0 (1.0) vs. –2.3 (0.6)] and height gain compared with H_0SDS [0.5 (0.9) vs. 0.3 (0.6)] were not significantly different between treated and control subjects. In the GH+GnRHa group, 53% reached a FH>–2.0 SDS, compared with 33% of control patients (difference not statistically significant). The treated subjects attained a FH closer to TH than controls [–6.0 (7.2) vs. –11.2 (5.7) cm; p<0.05], but mean FH of treated subjects was still significantly lower than TH (p<0.01).

Height gain (FH–PAH_0) was 4.4 (4.9) in the treatment and –0.5 (6.4) cm in the control group (fig. 2b). Of the predicted 9.3 cm gain in PAH (PAH_3–PAH_0) approximately 50% was lost during follow up (fig. 2), resulting in a net gain of 4.9 cm in the treatment group, compared to controls. Seventy-six percent of the GH+GnRHa treated children and 60% of the controls had a FH greater than predicted at baseline.

Height gain was similar in both genders, but there was a difference in the accuracy of the height prediction method between genders. Untreated boys attained a FH 5.5 (4.1) cm lower than predicted at baseline, whereas untreated girls became 1.9 (6.0) cm taller. Treated girls had a FH significantly closer to TH than controls ($p<0.05$), whereas no significant difference existed between treated and untreated boys.

Linear regression analysis of predictors for growth response

Gender was a predictor for the treatment effect (GH+GnRHa∗gender) expressed in FH–TH, with girls showing a better response than boys (regression coefficient B=10.7, CI=1.3–20.2, $p<0.05$; graph not shown). Age at baseline showed a trend towards a positive interaction with treatment effect (GH+GnRHa∗Age_0) in the outcome parameters FH SDS minus H_0SDS (B=0.7, CI= –0.01–1.5, $p<0.1$), and FH SDS minus PAH_0 SDS (B=0.8, CI= –0.1–1.7; $p<0.1$). Baseline height and diagnostic subgroup were no significant predictors for treatment effect in any of the outcome parameters.

Side effects

Lumbar spine and hip BMD were determined in 21 patients (69%), 15 treated and 6 control subjects; the others could not be motivated. There was no apparent difference in lumbar spine and hip BMD SDS between treated and untreated children (fig. 3a, c). Lumbar spine BMD SDS was markedly lower in the six treated boys (–2.5 (1.0) SDS), than in the two controls (–1.1 (0.3) SDS) who consented to undergo this diagnostic procedure (p=0.1; CI=–0.5-3.3). This difference was statistically not significant due to the small sample size of the control group (n=2). Lumbar spine BMAD showed a similar, albeit less prominent pattern (fig. 3b). BMI SDS remained unchanged during and after GH+GnRHa treatment in boys and girls.

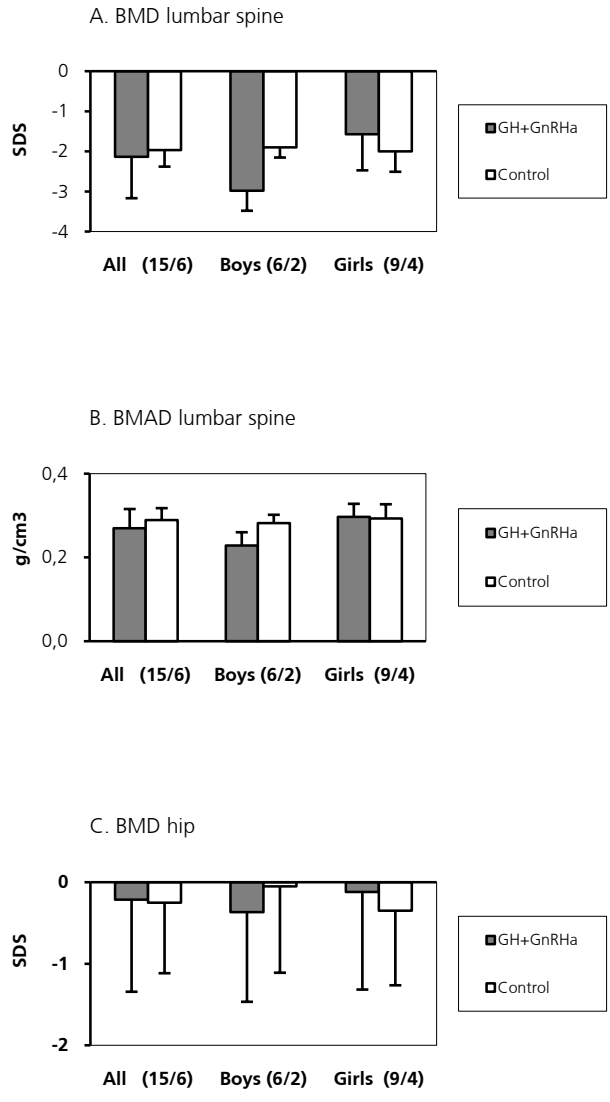
Table 1. Summary of initial and outcome variables (mean (SD))

Parameter	All			Boys			Girls		
	GH+GnRHa (n=17)	Control (n=15)	R_x vs. Co	GH+GnRHa (n=6)	Control (n=5)	R_x vs. Co	GH+GnRHa (n=11)	Control (n=10)	R_x vs. Co
Boys/girls	6/11	5/10							
SGA/ISS	6/11	5/10		2/4	2/3		4/7	3/7	
Start treatment									
Age_0 (yr)	11.6 (0.7)	11.8 (0.7)	ns	11.9 (0.8)	12.5 (0.6)	ns	11.4 (0.6)	11.5 (0.5)	ns
Bone age delay (yr)	0.7 (1.0)	1.0 (0.7)	ns	1.1 (1.0)	1.2 (0.7)	ns	0.5 (0.9)	0.9 (0.8)	ns
H_0 (cm)	135.4 (4.5)	136.1 (4.5)	ns	133.1 (3.8)	138.4 (5.8)	ns	136.7 (4.5)	134.9 (3.4)	ns
H_0SDS	-2.4 (0.5)	-2.5 (0.5)	ns	-2.7 (0.4)	-2.5 (0.5)	ns	-2.3 (0.5)	-2.6 (0.5)	ns
PAH_0 (cm)	157.4 (8.3)	160.0 (10.1)	ns	166.7 (4.9)	170.7 (8.7)	ns	152.4 (5.6)	154.7 (5.6)	ns
PAH_0SDS	-2.7 (0.7)	-2.3 (1.0)	ns	-2.5 (0.7)	-1.9 (1.2)	ns	-2.8 (0.7)	-2.5 (0.9)	ns
TH (cm)	167.4 (10.0)	170.7 (5.8)	ns	176.9 (9.6)	174.9 (4.1)	ns	163.1 (6.9)	168.6 (5.5)	ns
BMI_0SDS	-0.6 (0.9)	-0.5 (1.0)	ns	-0.7 (1.4)	0.0 (0.5)	ns	-0.6 (0.5)	-0.8 (1.0)	ns
Discontinuation of treatment									
Age_3 (yr)	14.9 (0.7)	14.6 (0.7)	ns	15.4 (0.6)	14.9 (0.8)	ns	14.6 (0.5)	14.4 (0.6)	ns
H_3 (cm)	154.6 (5.5)	152.9 (5.4)	ns	159.7 (6.7)	152.1 (5.9)	ns	152.1 (2.5)	153.3 (5.3)	ns
H_3SDS	-2.1 (0.8)	-2.2 (0.4)	ns	-2.7 (0.7)	-2.2 (0.6)	ns	-1.8 (0.7)	-2.1 (0.3)	ns
PAH_3 (cm)	166.7 (8.1)	161.3 (9.5)	P<0.1	174.0 (6.9)	169.3 (12.3)	ns	162.8 (5.8)	157.3 (4.6)	p<0.05
PAH_3SDS	-1.3 (0.9)	-2.1 (1.1)	p<0.05	-1.4 (1.0)	-2.1 (1.7)	ns	-1.2 (0.9)	-2.1 (0.7)	p<0.05
BMI_3SDS	-0.3 (1.0)	-0.4 (1.1)	ns	0.0 (1.1)	-0.6 (1.8)	ns	-0.5 (1.1)	-0.2 (0.4)	ns
At final height									
Age_f (yr)	20.3 (1.6)	20.2 (1.8)	ns	20.4 (0.8)	21.5 (1.0)	ns	20.2 (1.9)	19.5 (1.7)	ns
Final height (cm)	161.8 (6.3)	159.5 (5.7)	ns	165.6 (5.7)	165.2 (5.1)	ns	159.8 (5.8)	156.6 (3.3)	ns
FHSDS	-2.0 (1.0)	-2.3 (0.6)	ns	-2.6 (0.8)	-2.7 (0.7)	ns	-1.7 (0.9)	-2.2 (0.5)	ns
FH-H_0 (SDS)	0.5 (0.9)	0.3 (0.6)	ns	0.2 (0.7)	-0.2 (0.4)	ns	0.6 (1.0)	0.4 (0.6)	ns
FH-PAH_0 (cm)	4.4 (4.9)	-0.5 (6.4)	p<0.05	-1.0. (2.4)	-5.5 (4.1)	p<0.1	7.4 (3.0)	1.9 (6.0)	p<0.05
FH-PAH_3 (cm)	-4.9 (3.8)	-1.8 (4.9)	p<0.1	-8.3 (3.1)	-4.0 (7.4)	ns	-3.0 (2.8)	-0.7 (3.0)	p<0.1
FH-TH (cm)	-6.0 (7.2)	-11.2 (5.7)	p<0.05	-11.8 (6.5)	-9.7 (6.9)	ns	-3.3 (5.9)	-12.0 (5.3)	p<0.05
BMI_fSDS	0.0 (0.8)	0.1 (0.9)	ns	-0.4 (0.9)	0.3 (1.2)	ns	-0.3 (0.5)	0.0 (0.7)	ns

Mean (SD). Rx, treatment with GH+GnRHa; Co, no treatment; ns, no significant difference.

Figure 3

Effect of GH+GnRHa treatment on (a) lumbar spine BMD expressed as Z-score, (b) lumbar spine BMAD expressed in g/cm^3, and (c) total hip expressed as Z-score. Error bars represent standard deviations.



Discussion

We report final height results of the first RCT of combined GH+GnRHa treatment in short boys and girls, that includes a non-treated control group. Treatment resulted in a modest increase of approximately 5 cm compared to controls, as documented by difference between obtained adult height and initial predicted adult height and target height. The reason that the differences in final height SDS as such and the change in height SDS were not statistically significant is probably that the predicted adult height at start, as well as the target height, of the children randomly allocated to the treatment group happened to be approximately 3 cm lower than in controls.

Two previously published studies employed untreated controls as reference group. Saggese *et al.* found an increase in PAH of 6.1 cm after two years of GH+GnRHa in 7 ISS girls compared with controls (27). In contrast, Lanes and Gunczler (9) found no improvement in PAH or FH after 2.5 years of treatment in 10 short boys and girls. Other studies with different experimental designs showed similarly contrasting results on growth, varying from no effect on FH or PAH gain in girls with familial short stature (8) and in ISS boys and girls (14), to 10.5 cm gain in PAH and 10 cm height gain ($FH–PAH_0$) in ISS girls (12). These studies and ours cannot easily be compared due to differences in experimental design. GH+GnRHa trials in short adopted girls showed an increased PAH, $FH–PAH_0$ and FH compared with GnRHa-treated controls (10;13). Mul *et al.* suggested that the relevance of their results in adopted girls might be extrapolated to girls born SGA and those with ISS (10). Indeed, in our trial we found significantly increased PAH, height gain and FH compared with TH in the treated girls.

Approximately 50% of the apparent gain in PAH during treatment was lost during follow up. Initial height prediction overestimated FH in untreated boys, which has also been described by others (28). Height gain in terms of $FH–PAH_0$ is similar in both genders, although the accuracy of height prediction depends on gender. Untreated boys attain a FH considerably lower than predicted at baseline, whereas girls become slightly taller. Prediction at discontinuation of treatment overestimated final height, regardless of gender. A longer duration of combined therapy might further increase height gain, but would delay puberty even longer, up to an age that would far exceed the normal range. This might cause adverse effects on psychological and bone parameters. However, prolonging GH treatment after discontinuation of combined treatment until FH may be a way to fulfil part of the height gain predicted in PAH_3.

Gender did not influence the response to GH+GnRHa in three out of four outcome parameters. Only for FH–TH a better response to treatment was seen in girls. Previously published reports on GH+GnRHa treatment were usually conducted in short girls only, except a few small trials

including both genders (9;14). The inclusion of boys in our trial, might explain a somewhat lower overall response to treatment compared to other studies on GH+GnRHa treatment in short girls. The predictive value of gender on height outcome is limited in this study, since an effect was found in only one outcome measure (FH-TH).

We included an SGA subgroup, even though this category of patients was excluded from the 1996 consensus definition of ISS (29) and from most of the previously published studies. In our opinion the distinction between ISS and idiopathic SGA is arbitrary, due to varying definitions and reference values for length and weight for gestational age. In the ISS consensus, SGA was defined as a birth weight and/or length <–2.0 SDS for gestational age. This definition implies that a child with a birth weight in the lower normal range, may be categorized as ISS in case of an unknown birth length, and as SGA if birth length would be recorded as <–2.0 SDS. Moreover, the Gaussian distribution of birth weight and length in ISS is shifted to the left by 1 SDS (30), suggesting that persistent short stature born SGA and ISS are not separate entities. SGA and ISS children in our study had a similar response to treatment, demonstrating that diagnostic subgroup did not interact with the treatment effect. Similarly, Crowe *et al.* found no difference in response to GH treatment between SGA or ISS groups (31). However, patient numbers in our subgroups were small and larger sample numbers are required to analyze response to definitely confirm or reject our hypothesis that SGA and ISS children respond similarly to combined GH+GnRHa treatment.

Apart from beneficial effects on height gain, GH+GnRHa treatment may also have adverse effects. Palmert *et al.* found an elevated BMI in GnRHa-treated girls with central precocious puberty (CPP) (32). We did not find an increased BMI, neither directly after discontinuation of treatment (16) nor at final height analysis. The stimulatory effect of GnRHa on fat mass induction may have been counterbalanced by an adverse effect of GH in the treated children. The elevated BMI in GnRHa-treated girls from the American trial was possibly associated with precocious puberty itself rather than with the treatment.

A more relevant possible side-effect of GnRHa treatment was described by Yanovski *et al.* (33), who found a significantly decreased lumbar spine BMD after 4 years GnRHa treatment, with or without GH, of children with short stature based on various etiologies. A similar result was reported after 3.4 years of GnRHa treatment in girls with ISS (34). In GnRHa-treated children with CPP, lumbar spine BMD was significantly decreased during treatment (35), but restored to normal values several years after withdrawal of treatment (34;35), suggesting that GnRHa-therapy did not impair peak bone mass in this subcategory of patients. In contrast, Finkelstein *et al.* demonstrated that adult men with a history of delayed puberty had a decreased radial and spinal BMD (36), suggesting that the timing of puberty is an important determinant of peak

bone density in men. BMD achieved during young adulthood might be a major determinant of bone density and a predictor for the risk of osteoporotic fractures in later life.

In our study, there was no apparent difference between treatment and control groups in lumbar spine and hip BMD measured at least 3.5 years after termination of treatment. However, the six treated boys had a lower lumbar spine BMD and BMAD than the 2 untreated boys, albeit statistically not significant. A meta-analysis by Marshall *et al*. demonstrated that with each 1 SDS decrease in lumbar spine BMD, fracture risk increased 2.3 fold (37). Therefore, we believe that there is sufficient reason to be cautious when considering GH+GnRHa treatment in boys. On the other hand, it has been shown that after interruption of skeletal development in childhood, there is still potential for catch-up in BMD, even ongoing into the third decade of life (38;39). Taking this into account, it remains to be seen whether the low lumbar spine BMD in treated boys has clinical repercussions and whether it will restore to normal values.

In girls, there was no difference in lumbar spine and hip BMD between treated and control groups. This may be explained by an immediate rise in estrogen to high levels after treatment withdrawal in girls, favoring bone mineralization. In boys, the post-treatment rise in estrogen levels may be slower and reach a lower maximum, resulting in a later and possibly lesser stimulation of bone mineralization.

Apart from these clinical issues, psychosocial issues should also be taken into account. Analyses of psychosocial functioning during treatment tentatively suggested adverse psychological consequences for the treated adolescents on self-perceived competence of scholastic and athletic ability, and trait anxiety (17). Parents reported some behavioral problems in their children before treatment (18), but did not report changes during treatment. Psychosocial outcome after attaining final adult height was one of the final evaluation criteria of this trial and so far no differences have been observed between treatment and control groups in social circumstances, height-related psychosocial stressors, perceived competence, and psychological distress in young adulthood (Visser-van Balen, submitted for publication).

We conclude that 3 years of GH+GnRHa treatment has a positive, but modest effect of 4.9 cm on final height in short, early pubertal children with ISS or a persistent short stature born SGA, compared with non-treated controls. The costs of long term treatment with GH+GnRHa of short, but otherwise healthy patients, with extremely expensive drugs that require parenteral administration and regular clinic visits, and may have an adverse effect on peak bone mineralization, particularly in males, overshadows the modest benefit of 4.9 cm height gain. We therefore do not recommended this treatment regimen in general. However, treatment may be felt justified in individual patients, particularly girls, with an extremely low adult height prediction, an early pubertal onset and considerable psychosocial problems.

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