Randomized Controlled Trial to Investigate the Effects of Growth Hormone Treatment on Scoliosis in Children with Prader-Willi Syndrome

Roderick F. A. de Lind van Wijngaarden, Luuk W. L. de Klerk, Dederieke A. M. Festen, Hugo J. Duivenvoorden, Barto J. Otten, and Anita C. S. Hokken-Koelega

Dutch Growth Research Foundation (R.F.A.d.L.v.W., D.A.M.F., A.C.S.H.-K.), 3016 AH Rotterdam, The Netherlands; Departments of Pediatric Endocrinology (R.F.A.d.L.v.W., D.A.M.F., A.C.S.H.-K.), and Pediatric Orthopedic Surgery (L.W.L.d.K.), Erasmus University Medical Center/Sophia Children's Hospital, 3015 GJ Rotterdam, The Netherlands; The Netherlands Institute for Health Sciences (H.J.D.), Erasmus University Rotterdam, 3015 GE Rotterdam, The Netherlands; and Department of Pediatric Endocrinology (B.J.O.), University Medical Center St. Radboud, 6525 GA Nijmegen, The Netherlands

Context: The prevalence of scoliosis in children with Prader-Willi syndrome (PWS) is 30–80%, depending on age. Although reports about effects of GH treatment on scoliosis in children with PWS are limited, scoliosis is generally considered a contraindication for GH treatment.

Objective: The aim was to study the effects of GH treatment on the onset of scoliosis and curve progression in children with PWS.

Design: We conducted a multicenter, randomized, controlled GH study in infants and prepubertal and pubertal children. Infants and prepubertal children were randomized into a GH-treated group (1.0 mg/m^2 · d) and a control group for 1 and 2 yr, respectively. Pubertal children were randomized to receive somatropin 1.0 or 1.5 mg/m^2 · d. Yearly, x-rays of the spine were taken, and height, weight, truncal lean body mass (with dual energy x-ray absorptiometry), and IGF-I were measured.

Patients: A total of 91 children with PWS (median age, 4.7 yr; interquartile range, 2.1–7.4) participated in the study.

Main Outcome Measures: We measured the onset of scoliosis (Cobb >10°) and scoliotic curve progression.

Results: GH-treated children had similar onset of scoliosis and curve progression as randomized controls (P = 0.27–0.79 and P = 0.18–0.98, respectively). GH treatment, IGF-I SD score (SDS), and catch-up growth had no adverse effect on the onset of scoliosis or curve progression, even after adjustment for confounders. Height SDS, truncal lean body mass, and IGF-I SDS were significantly higher in GH-treated children than in randomized controls. At baseline, a higher IGF-I SDS was associated with a lower severity of scoliosis.

Conclusions: Scoliosis should no longer be considered a contraindication for GH treatment in children with PWS. (***J Clin Endocrinol Metab*** **94: 1274–1280, 2009)**

Prader-Willi syndrome (PWS) is characterized by hypotonia, short stature, hyperphagia with obesity, hypogonadism, and psychological and behavioral problems (1–7). PWS results from lack of expression of the paternally derived chromosome 15q11-q13 caused by deletion, uniparental disomy, imprinting center defect, or balanced translocation (1, 8). Hypothalamic dysfunction may be responsible for many features of PWS (9–11).

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2008-1844 Received August 22, 2008. Accepted January 9, 2009.
First Published Online January 21, 2009

Abbreviations: BMI, Body mass index; BSA, body surface area; CI, confidence interval; iqr, interquartile range; IS, idiopathic scoliosis; LCS, long C-curve type scoliosis; OR, odds ratio(s); PWS, Prader-Willi syndrome; SDS, SD score; trunkLBM, truncal lean body mass.

Spinal deformity is a major concern for patients with PWS. Scoliosis is defined as a spinal curve with a Cobb angle of more than 10° on a standing posteroanterior radiograph. The Cobb angle is the angle between the two steepest vertebrae, *i.e.* the upper border of the upper vertebra in the curve and the lower border of the lower vertebra (12). The prevalence of scoliosis in PWS is high [30% before 10 yr of age, 80% after age 10 yr (13–15) *vs.* 2.7% in the general Dutch adolescent population (16)]. Children with PWS show two types of scoliosis (Fig. 1): long C-curve type scoliosis (LCS), often seen in children with neuromuscular disorders causing hypotonia; and scoliosis resembling idiopathic scoliosis (IS). Young children mainly show LCS, associated with a low ratio of truncal lean body mass (trunkLBM) to body surface area (BSA), which is a proxy for hypotonia. Older children mainly show IS (13).

GH treatment is beneficial for children with PWS because it improves body composition (increase in lean body mass, decrease in fat percentage) and psychomotor development (17–23). In a previous report by our group, the effects of GH treatment on height and body composition of children with PWS have been described in detail (23). Accelerated growth, either spontaneous or during GH treatment, has been associated with the onset of scoliosis and scoliotic curve progression (24–29). Because scoliosis is often considered a contraindication for GH treatment in children with PWS, the need for controlled data about the effect of GH treatment on scoliosis was emphasized (30–32). We therefore performed a large randomized controlled trial. We hypothesized that GH treatment would not affect scoliosis because it also increases trunkLBM, which may counteract the adverse effects of accelerated growth on scoliosis. The primary aim of our study was to investigate the effects of GH treatment on the onset of scoliosis. The secondary aim was to study the effects of GH treatment on scoliotic curve progression. Because age and gender are known to affect the onset of scoliosis, whereas age, gender, and severity of scoliosis affect curve progression, we adjusted for these factors in our analyses.

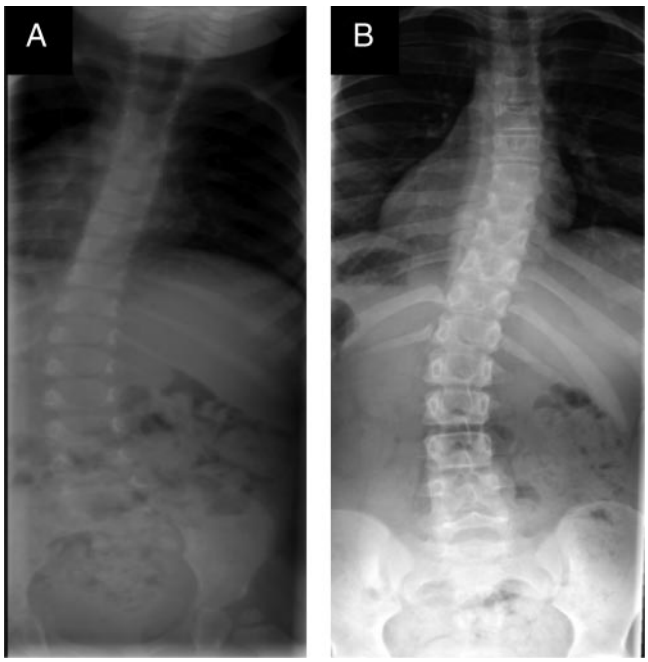

FIG. 1. Examples of LCS (A) and IS (B). Younger children mainly showed LCS, whereas pubertal children only showed IS.

Subjects and Methods

Subjects

Between April 2002 and January 2008, 104 children were enrolled in a large randomized controlled trial investigating the effects of GH treatment in children with PWS (Table 1), after fulfilling the following inclusion criteria: genetically confirmed diagnosis of PWS by positive methylation test and age between 6 months and 16 yr. The participants were divided into three groups: infants, prepubertal children, and pubertal children. The infant group consisted of children aged 6 months to 3.5 yr. The prepubertal group consisted of girls aged 3.5 to 12 yr with Tanner breast stage less than 2 (33) and boys aged 3.5 to 14 yr with Tanner genital stage less than 2 and a testicular volume below 4 ml. The pubertal group consisted of girls aged 12 to 16 yr and boys aged 14 to 16 yr with spontaneous or induced puberty. Caloric intake and activity level of all participants were standardized. All children were naive to GH treatment at the start of the study. Children visited the Erasmus University Medical Center/Sophia Children's Hospital in Rotterdam, The Netherlands, and the study protocol was approved by the Medical Ethics Committee. Written informed consent was obtained from parents and children over 12 yr of age. Assent was obtained for children between 4 and 12 yr of age.

Design

The primary objective of our study was to investigate the effects of GH treatment on the onset of scoliosis. The secondary objective was to study the effects of GH treatment on progression of scoliosis. Infants and prepubertal children were randomized into a GH-treated group (1.0 $mg/m^2 \cdot d$) and a control group for 1 and 2 yr, respectively. Pubertal children were randomly assigned to receive somatropin 1.0 or 1.5 $mg/m^2 \cdot d$ (Genotropin; Pfizer, New York, NY) for a follow-up period of 2 yr. During the first 4 wk of treatment, children received 0.5 $mg/m^2 \cdot d$ to prevent fluid retention. In January 2008, 38 infants (<3.5 yr) had completed the 1-yr follow-up, and 44 prepubertal and nine pubertal children had completed the 2-yr follow-up. Thus, 91 children were eligible for analysis (Table 1).

Radiographics

At the start and subsequently each year, standardized posteroanterior x-rays were taken. In young and/or hypotonic children who were not able to sit or stand, posteroanterior x-rays were taken in the supine position. All x-rays were taken in one center (Erasmus University Medical Center Rotterdam/Sophia Children's Hospital). Cobb angles were measured independently by two observers (R.F.A.d.L.v.W. and L.W.L.d.K.), as previously reported, with minimal intra- and interobserver variance (intraclass correlation coefficient = 0.998 and 0.97, respectively) (13). The orthopedic surgeon was fully blinded to the assigned treatment. If the independent measurements of Cobb angles differed between the two observers, the mean of the Cobb angles was used for analysis. Onset of scoliosis was defined as the presence of a Cobb angle of 10° or higher at 12 or 24 months of study in those without scoliosis at baseline (outcome: yes/no). Progression of scoliosis was evaluated as the change in Cobb angle over time in those with scoliosis at baseline and in those that developed scoliosis during study. Because treatment of scoliosis (bracing and surgery) prevents further curve progression, the effects of GH treatment on curve progression were only investigated in children with untreated scoliosis. For baseline characteristics of the total study population (Table 1), the Cobb angle of the scoliotic curve of children treated with a brace was set at 35°, and the Cobb angle of those surgically treated at 55°. None of the children needed to start treatment of scoliosis during the study.

TABLE 1. Baseline data

	Total	Infants		Prepubertal		Pubertal	
		GH-treated	Controls	GH-treated	Controls	GH-treated (1.0 mg/m² · d)	GH-treated (1.5 mg/m² · d)
No. of subjects (M/F)	91 (49/42)	19 (11/8)	19 (14/5)	23 (13/10)	21 (8/13)	6 (3/3)	3 (0/3)
Age (yr)	4.7 (2.1 to 7.4)	2.0 (1.6 to 3.1)	1.5 (1.1 to 3.0)	6.8 (5.6 to 9.7)	6.0 (4.6 to 7.5)	13.4 (11.8 to 15.9)	13.9 (12.0 to 14.8)
Height SDS	−2.2 (−3.1 to −1.3)	−2.5 (−2.8 to −0.6)	−2.0 (−3.2 to −0.9)	−1.9 (−2.8 to −0.9)	−2.6 (−3.3 to −1.9)	−3.7 (−4.0 to −2.9)	−2.4 (−4.8 to −1.8)
BMI SDS	1.1 (−0.6 to 1.9)	−0.7 (−1.1 to 1.5)	−0.8 (−1.7 to 1.7)	1.2 (0.2 to 2.6)	1.2 (1.1 to 1.7)	1.2 (−0.1 to 2.1)	1.6 (−0.6 to 1.7)
TrunkLBM:BSA	7.6 (7.2 to 8.1)	7.4 (6.9 to 8.0)	7.3 (7.0 to 7.7)	8.0 (7.5 to 8.4)	7.6 (7.1 to 8.1)	8.7 (8.1 to 8.9)	8.1 (7.5 to 8.4)
IGF-I SDS	−2.1 (−3.1 to −1.4)	−2.5 (−3.9 to −1.4)	−2.6 (−5.7 to −0.7)	−1.7 (−2.3 to −1.2)	−1.9 (−2.6 to −1.2)	−3.0 (−4.9 to −2.5)	−2.1 (−3.3 to −2.0)
Scoliosis (%)	33 (36)	7 (37)	4 (21)	7 (30)	9 (43)	4 (67)	2 (67)
LCS-type (%)	13 (37)	3 (43)	3 (75)	2 (25)	5 (50)	0 (0)	0 (0)
IS-type (%)	22 (63)	4 (57)	1 (25)	6 (75)	5 (50)	4 (100)	2 (100)
Treated for scoliosis (%)	12 (13)	1 (5)	1 (5)	3 (13)	2 (10)	4 (100)	1 (33)
Cobb angle (°)	19.0 (13.3 to 36.0)	15.5 (14.0 to 25.5)	18.5 (13.8 to 46.1)	14.5 (12.0 to 55.0)	16.0 (12.8 to 20.5)	36.0 (35.0 to 50.5)	21.3 (13.0 to 29.5)

Overview of study population. Data represent number (percentage) or median (iqr). TrunkLBM:BSA, ratio of trunkLBM divided by body surface area (kg/m²); scoliosis (LCS/IS), total number of children with scoliosis and the number of children divided by type of scoliosis; treated for scoliosis, total number of children treated for scoliosis and the percentage of children with treated scoliosis within the total group of children. At baseline, there were no significant differences between GH-treated children and randomized controls. M, Males; F, females.

Anthropometrics

Standing height was measured with a Harpenden Stadiometer and supine length with a Harpenden Infantometer (Holtain Ltd., Crosswell, UK). Weight was assessed on an accurate scale. Height and body mass index (BMI) SD scores (SDS) were calculated, adjusted for sex and age according to Dutch references (34, 35). Height SDS, BMI SDS, and BSA were calculated with Growth Analyser 3.0 (available at www.growthanalyser.org). Growth was calculated as the increase in height SDS per year (ΔheightSDS) or the increase in centimeters per year (Δheight).

Severe scoliosis interferes with height and therefore also with ΔheightSDS. Lean body mass is known to be highly correlated with height (23, 36, 37). In our study, these two parameters also showed a strong correlation (rho = 0.82, $P < 0.0001$; and rho = 0.67, $P < 0.0001$ at 12 and 24 months, respectively). To analyze the effect of Δheight on the onset of scoliosis and curve progression, we therefore also used the change in trunkLBM (ΔtrunkLBM) as a proxy for Δheight.

Dual energy x-ray absorptiometry

Dual energy x-ray absorptiometry (type Lunar Prodigy; GE Healthcare, Chalfont St. Giles, UK) was performed to measure the trunkLBM, defined as the total amount of lean body mass in the chest, abdomen, and pelvis. Reference values of trunkLBM in very young children were not available. To analyze the effects of GH treatment on relative muscle mass, we used a ratio of trunkLBM *vs.* BSA (trunkLBM:BSA ratio), as previously described (13).

Assay

Serum IGF-I levels were measured using an immunometric technique on an Advantage Automatic Chemiluminescence System (Nichols Institute Diagnostics, San Juan Capistrano, CA).

The intraassay coefficient of variation was 4%, and the interassay coefficient of variation was 6%. Because of age and sex dependency, IGF-I levels were transformed into SDS (38).

Data analysis

Data were analyzed for all children together as well as for different age categories. Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS 15.0; SPSS Inc., Chicago, IL). Data are presented as median and interquartile range (iqr). A change in Cobb angle of 5° or more was considered clinically relevant. Power calculation estimated a total number of 40 patients (comprising infants and prepubertal children) to yield a power of 0.80, in line with the international convention: assuming a clinically relevant difference between GH-treated children and controls of 0.80 in terms of Cohen's d, an α level of 0.05 (one-tailed) and a total number of required patients of 40, the power of the study was 0.80 (39). In our primary analyses, effects of GH treatment on onset and progression of scoliosis were analyzed after adjustment for confounders, using binary logistic regression models for onset of scoliosis [see Table 3, odds ratio (OR)] and linear regression models for curve progression (see Table 4, in β). To allow comparison with other reports regarding scoliosis in PWS in which these adjustments were not performed, we additionally analyzed differences in onset of scoliosis and curve progression between GH-treated children and randomized controls with χ^2 tests and Mann-Whitney *U* tests.

To investigate the risk of onset of scoliosis during the study, we included all children without scoliosis at the start of the study. Goodness of fit of binary logistic regression models was assured by performing the Hosmer and Lemeshow test (correct fitting when $P > 0.05$). R^2 was calculated as a measure of explained variance. To investigate curve progression, we included all children with untreated scoliosis at the start of the study and those who had their onset of scoliosis during the study. Tolerance of all variables within the linear regression models was assured by calculating the variable inflation factor as a measure of multicollinearity. Nagelkerkes R^2 was calculated for all binary logistic and R^2 for all linear regression models as a measure of explained variance.

Mann-Whitney *U* tests and χ^2 tests were performed to compare outcomes between two groups. Data obtained in the smaller pubertal group were analyzed separately. A P value <0.05 was considered statistically significant.

Results

Table 1 shows the baseline clinical characteristics of the 91 children with PWS in our randomized controlled trial who completed the 1- or 2-yr follow-up. The median (iqr) age was 4.7 yr (2.1–7.4). The genotype was specified in 77 children: 35 had a deletion (46%), 33 had an uniparental disomy (43%), eight had an imprinting center defect (10%), and one had a balanced translocation (1%). Positive methylation test was demonstrated in the remaining 14 patients, but the underlying genetic defect was not identified.

Baseline data

At the start of the study (Table 1), 36% of children had scoliosis with a median (iqr) Cobb angle of 19.0° (13.3°-36.0°). The prevalence of scoliosis increased with age (infants *vs.* pubertal, $P = 0.03$). With increasing age, there was a shift from a predominance of LCS type (Fig. 1) in infants toward a predominance of scoliosis resembling IS type (Fig. 1) in older children (infants *vs.* pubertal, $P < 0.03$). The differences in prevalence of scoliosis and predominance of IS type between prepubertal and pubertal children did not reach statistical significance, most likely due to the limited number of pubertal children ($P = 0.09$ and $P = 0.07$, respectively). The number of children treated for scoliosis was higher in older children.

Prepubertal children had a significantly higher BMI SDS than infants ($P < 0.0001$). Pubertal children also had a higher BMI SDS than infants, but this did not reach statistical significance ($P = 0.07$). Prepubertal children had a significantly higher IGF-I SDS compared with pubertal children ($P = 0.004$) and compared with infants, but this did not reach statistical significance ($P = 0.06$). The trunkLBM:BSA ratio increased with age and was significantly different between all age categories ($P < 0.0001$ to $P = 0.02$).

Children who were treated for scoliosis at the start of the study had lower IGF-I SDS than children without scoliosis [−3.3 (−4.5 to −2.1) *vs.* −2.0 (−2.8 to −1.3), $P = 0.02$], suggesting a protective effect of higher IGF-I levels. Linear regression modeling for 91 children at the start of the study showed a tendency for a less severe scoliosis in case of higher IGF-I levels (age: $\beta = 3.83$, $P = 0.059$; IGF-I SDS: $\beta = -0.26$, $P = 0.08$).

Effects of GH treatment on growth and IGF-I levels

At baseline, there were no significant differences in age, height SDS, BMI SDS, trunkLBM:BSA ratio, IGF-I SDS, and prevalence and severity of scoliosis between the GH treatment group and the randomized controls. In all children, GH treatment significantly increased height SDS and IGF-I SDS compared with randomized controls (Table 2). Growth in prepubertal GH-treated children was greatest during the first year: median (iqr) ΔheightSDS, 0.9 (0.7–1.3) during the first year *vs.* 0.6 (0.3–0.7) during the second

TABLE 2. Effects of GH treatment *vs.* randomized controls

	Prepubertal									
	Infants (at 12 months)			At 12 months			At 24 months			
	GH-treated	Controls	P[a]	GH-treated	Controls	P[a]	GH-treated	Controls	P[a]
n	19	19		23	21		23	21	
Height SDS	−0.9 (−1.6 to 0.1)	−1.8 (−3.5 to −1.4)	**0.003**	−1.0 (−1.5 to −0.3)	−2.5 (−3.4 to −2.3)	**<0.0001**	−0.5 (−0.8 to 0.0)	−2.6 (−3.4 to −2.3)	**<0.0001**
ΔheightSDS	1.2 (1.0 to 1.6)	−0.2 (−0.6 to 0.3)	**<0.0001**	0.9 (0.7 to 1.3)	−0.1 (−0.2 to 0.1)	**<0.0001**	1.4 (1.3 to 1.8)	−0.1 (−0.4 to 0.1)	**<0.0001**
BMI SDS	0.3 (−0.1 to 1.6)	0.3 (−0.6 to 1.6)	0.72	0.8 (−0.1 to 2.1)	1.4 (1.0 to 1.6)	0.05	1.1 (−0.2 to 1.7)	1.4 (1.1 to 1.6)	0.19
ΔtrunkLBM	1.7 (1.3 to 2.1)	0.7 (0.4 to 0.9)	**<0.0001**	1.8 (1.4 to 2.3)	0.7 (0.1 to 0.8)	**<0.0001**	2.8 (2.6 to 3.5)	0.8 (0.4 to 1.0)	**<0.0001**
ΔtrunkLBM:BSA	1.2 (0.7 to 1.8)	0.3 (−0.3 to 0.6)	**0.002**	1.3 (0.7 to 1.7)	0.0 (−0.4 to 0.3)	**<0.0001**	1.4 (0.5 to 1.7)	−0.2 (−0.5 to −0.1)	**<0.0001**
IGF-I SDS	2.5 (1.4 to 2.9)	−2.6 (−4.1 to −0.7)	**<0.0001**	2.3 (1.5 to 2.8)	−2.5 (−3.1 to −1.5)	**<0.0001**	2.4 (2.1 to 2.8)	−1.6 (−2.5 to −1.0)	**<0.0001**
Onset scoliosis (%)	4 (21)	2 (11)	0.71	5 (22)	6 (29)	0.52	5 (22)	7 (33)	0.14
Progression	−6.0 (−12.5 to 12.8)	−7.5 (−7.5 to −5.0)	0.48	−3.5 (−7.3 to 1.8)	0.0 (−1.0 to 1.0)	0.60	3.3 (−4.3 to 11.9)	−5.0 (−9.0 to −2.0)	0.27

Effects of GH treatment on different parameters expressed as median (iqr) or number (%). ΔheightSDS, ΔtrunkLBM, and ΔtrunkLBM:BSA are the gain in heightSDS, trunkLBM (kg), and trunkLBM:BSA ratio (kg/m^2) after 12 or 24 months of study compared to baseline. Progression is the change in Cobb angle during 12 or 24 months of study. Significant *P* values are shown in ***bold***.

[a] *P* values of Mann-Whitney *U* tests, GH-treated *vs.* controls.

TABLE 3. Odds ratios for the risk of onset of scoliosis

	Infants at 12 months (n = 27)						Prepubertal children (n = 28)											
							12 months						24 months					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*
Age	0.68	0.54	0.49	0.32	0.50	0.37	0.62	0.06	0.63	0.06	0.63	0.06	1.00	1.00	0.99	0.95	0.97	0.86
Gender	4.16	0.18	12.53	0.06	12.80	0.08	0.38	0.31	0.28	0.21	0.28	0.20	0.56	0.49	0.34	0.26	0.28	0.22
GH	3.33	0.26			0.89	0.96	0.42	0.36			1.46	0.80	0.28	0.13			2.81	0.59
ΔtrunkLBM			2.06	0.45	2.25	0.69			0.46	0.17	0.38	0.29			0.47	0.06	0.30	0.19
R^2		0.19		0.29		0.29		0.29		0.33		0.34		0.12		0.19		0.20

Binary logistic regression models depicting the effects of parameters on the risk of onset of scoliosis, expressed as OR. Gender: 0 = male, 1 = female. GH treatment: 0 = no GH treatment, 1 = GH treatment. ΔtrunkLBM, Increase in truncal muscle mass in kilograms; R^2, explained variance by the model.

year ($P < 0.0001$). Thus, catch-up growth was the most prominent during the first year of GH treatment. Compared with controls, BMI SDS tended to be lower in GH-treated children at 12 months of study ($P = 0.05$), but was not significantly different at 24 months of study ($P = 0.19$). GH treatment significantly decreased the hypotonia of the truncal muscles, shown by an increase in ΔtrunkLBM and ΔtrunkLBM:BSA ratio. There was a significant correlation between IGF-I SDS and trunkLBM:BSA ratio (r = 0.51 with $P < 0.0001$; and r = 0.41 with $P < 0.0001$, at 12 and 24 months of study, respectively). During our study, there were no adverse effects of GH treatment.

Effects of GH treatment on scoliosis

Infants (0 to 3.5 yr)

During 12 months of study, there was no significant difference between GH-treated infants and randomized controls with regard to onset of scoliosis, curve progression ($P = 0.71$ and $P = 0.48$; Table 2), and start of treatment for scoliosis ($P = 1.00$).

Table 3 shows the OR for the risk of onset of scoliosis. Corrected for age and gender, GH treatment had no significant effect on the risk of onset of scoliosis, with an OR [95% confidence interval (CI)] of 3.33 (0.41–27.2) ($P = 0.26$, model 1). Also, ΔtrunkLBM as a proxy for Δheight did not affect the risk of onset of scoliosis, with an OR (95% CI) of 2.1 (0.3–13.7) ($P = 0.45$, model 2). In our final model (model 3), both GH treatment and ΔtrunkLBM did not increase the risk of onset of scoliosis in infants with PWS.

Table 4 shows the effect (β) of different variables on the progression of scoliosis. Corrected for age and gender, IGF-I SDS had no significant effect on the progression of scoliosis during 12 months of study, with a β (95% CI) of 1.20 (−1.0 to 3.4) ($P = 0.24$, model 1). Also, ΔtrunkLBM as a proxy for Δheight did not affect the progression of scoliosis during 12 months of study [β (95% CI), 7.19 (−19.1 to 33.5), $P = 0.51$; model 2]. In our final model (model 3), IGF-I SDS, ΔtrunkLBM, and the severity of scoliosis at start of study had no significant effect on the progression of scoliosis in infants with PWS.

Results were similar when ΔheightSDS was included in our models instead of ΔtrunkLBM.

Prepubertal children (3.5 to 12/14 yr)

During 12 and 24 months of study, there was no significant difference between GH-treated prepubertal children and randomized controls with regard to onset of scoliosis, curve progression (12 months, $P = 0.52$ and $P = 0.60$; 24 months, $P = 0.14$ and $P = 0.27$; Table 2), and start of treatment for scoliosis (both $P = 1.00$).

Table 3 shows the OR for the risk of onset of scoliosis. Corrected for age and gender, GH treatment had no significant effect on the risk of onset of scoliosis after 12 and 24 months of study with an OR (95% CI) of 0.42 (0.07–2.7) at 12 months and 0.3 (0.05–1.5) at 24 months of study ($P = 0.36$ and $P = 0.16$, respectively; model 1). Also, ΔtrunkLBM as a proxy for Δheight did not affect the risk of onset of scoliosis after 12 and 24 months

TABLE 4. Multiple linear regression models (β) for influences on curve progression

	Infants, 0–12 months (n = 15)						Prepubertal children (n = 26)											
							0–12 months						12–24 months					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Age	3.05	0.34	4.75	0.40	4.73	0.44	−1.32	0.07	−0.87	0.24	−0.50	0.44	1.19	0.14	0.87	0.29	1.00	0.25
Gender	11.85	0.06	12.81	0.09	8.27	0.46	−2.94	0.40	−4.71	0.20	−3.29	0.30	3.32	0.35	4.98	0.19	5.18	0.18
IGF-I SDS	1.20	0.24	0.38	0.81	0.41	0.81	−0.24	0.69	0.59	0.47	0.45	0.52	1.36	0.09	0.03	0.98	−0.26	0.85
ΔtrunkLBM			7.19	0.51	7.84	0.52			−3.95	0.16	−4.13	0.09			2.91	0.22	3.30	0.18
Cobb at start					−0.47	0.59					−0.71	**0.03**					−0.24	0.52
R^2		0.47		0.52		0.56		0.28		0.37		0.57		0.25		0.31		0.33

Multiple linear regression models depicting the effects of parameters on curve progression, defined as the Cobb angle of the main scoliotic curve, expressed in β. Gender: 0 = male, 1 = female. ΔtrunkLBM, Increase in truncal muscle mass in kilograms; Cobb at start, Cobb angle of the scoliotic curve at start of study; R^2, explained variance by the model. Significant *P* values are shown in *bold*.

of study, with an OR (95% CI) of 0.46 (0.1–1.4) at 12 months and 0.47 (0.2–1.0) at 24 months of study ($P = 0.17$ and $P = 0.06$, respectively; model 2). In our final model (model 3), both GH treatment and ΔtrunkLBM did not increase the risk of onset of scoliosis in prepubertal children with PWS after 12 and 24 months of study.

Table 4 shows the effect (β) of different variables on the progression of scoliosis. Corrected for age and gender, IGF-I SDS had no significant effect on the progression of scoliosis during the first and second year of the study, with a β (95% CI) of −0.24 (−1.5 to 1.0) during the first year and 1.3 (−0.3 to 2.9) during the second year of study ($P = 0.69$ and $P = 0.10$, respectively; model 1). Also, ΔtrunkLBM as a proxy for Δheight did not significantly affect the progression of scoliosis, with a β (95% CI) of −3.95 (−9.6 to 1.8) during the first year and 3.7 (−3.9 to 11.3) during the second year of study ($P = 0.16$ and $P = 0.32$, respectively; model 2). In our final model with the highest explained variance (model 3, $R^2 = 0.57$), a more severe scoliosis at the start of the study and a higher ΔtrunkLBM during the first year were associated with a tendency for regression of scoliosis [β (95% CI) of ΔtrunkLBM, −4.1 (−9.1 to 0.8) with $P = 0.09$; β (95% CI) of severity at start, −0.71 (−1.30 to −0.11) with $P = 0.03$]. During the second year of GH treatment, IGF-I SDS, ΔtrunkLBM, and Cobb angle at start of study had no significant effect on curve progression in prepubertal children with PWS.

Results were similar when ΔheightSDS was included in our models instead of ΔtrunkLBM.

Pubertal children (12/14 to 16 yr)

A GH dose of 1.5 mg/m^2 · d in pubertal children (n = 3) resulted in a higher height velocity and IGF-I SDS compared with those treated with 1.0 mg/m^2 · d (n = 6; $P = 0.046$ and $P = 0.08$, respectively; data not shown). Three of nine pubertal children had no scoliosis at the start of the study and had no onset of scoliosis during the study. Six pubertal children had scoliosis at the start of the study, but there was no difference in the number of children treated for scoliosis or in curve progression between those treated with a dose of 1.0 and 1.5 mg/m^2 · d (data not shown).

Discussion

Our randomized controlled trial shows that there was no significant difference between GH-treated children and randomized controls with regard to onset of scoliosis, curve progression, and start of treatment of scoliosis. In both the infant and prepubertal groups, GH treatment, ΔheightSDS, ΔtrunkLBM (used as a proxy for Δheight), and IGF-I SDS were not associated with an increased risk of onset of scoliosis or curve progression, both before and after correction for confounders. Thus, GH treatment not only improves height SDS and trunkLBM of children with PWS (17–23), but it also has no adverse effects on the onset of scoliosis and curve progression.

Some authors have described an association between increased GH levels and a higher rate of curve progression in children without PWS (27–29). In contrast to these reports, our data show that a higher baseline IGF-I SDS was associated with a lower severity of scoliosis, suggesting a protective effect of higher IGF-I SDS in children with PWS. Because IGF-I SDS was also positively associated with the trunkLBM:BSA ratio, the protective effect may be due to a higher trunkLBM. In our randomized controlled trial, GH-treated children had a significantly higher IGF-I SDS and ΔtrunkLBM, but IGF-I SDS was not associated with the progression of scoliosis. The ΔtrunkLBM, however, was associated with a tendency for regression of scoliosis, but only during the first year of the study.

The prepubertal group provides the most accurate information about the effects of GH treatment on scoliosis because all x-rays were taken in standing position and children were followed in a 2-yr randomized controlled trial. GH treatment and catch-up growth had no adverse effect on the onset of scoliosis or curve progression. Notably, our results show that those with a more severe scoliosis at the start of the study and a higher catch-up growth had a tendency for regression of scoliosis during the first year of the study. This effect was not seen during the second year. Our study is the first randomized controlled trial investigating the effects of GH treatment on scoliosis in a large group of children with PWS. Our data indicate that even severe scoliosis should not be considered a contraindication for GH treatment in children with PWS. The findings are in line with a retrospective study demonstrating that GH treatment did not affect scoliosis in these children (14).

Although our main aim was to investigate the onset and progression of scoliosis in a randomized controlled GH trial in infants and prepubertal children, we did not want to withhold GH treatment from a small group of pubertal children with PWS. In this group of pubertal children, we found that a higher dose of GH (1.5 mg/m^2 · d) increased height velocity and IGF-I SDS and was not associated with an accelerated onset of scoliosis or curve progression.

Infants had a controlled period of 1 yr and prepubertal children of 2 yr. This period is not very long for follow-up. However, in orthopedic practice visits are scheduled every 4 to 6 months to monitor progression. Therefore, changes occurring during GH treatment can easily be noted during 1 or 2 yr of follow-up. Moreover, if GH treatment would have adverse effects on scoliosis by stimulating growth, one would especially notice this during the period with the highest gain in height SDS, *i.e.* catch-up growth during the first year of GH treatment. In our opinion, 1 or 2 yr of follow-up is sufficient to identify the effects of GH-induced catch-up growth on the onset or progression of scoliosis. Our final models in infants and prepubertal children explained 20–57% of variances (R^2). In the future, when more data on the pathogenesis of scoliosis become available, perhaps our models might be improved.

In conclusion, our randomized controlled GH trial in a large group of children with PWS shows that GH treatment had no adverse effects on the onset of scoliosis and curve progression. A higher baseline IGF-I SDS was associated with a lower severity of scoliosis. Thus, scoliosis should not be considered a contraindication for GH treatment in children with Prader-Willi syndrome. Because of the high prevalence of scoliosis and the potential associated morbidities in patients with PWS, it is recommended

to perform frequent physical examinations and yearly radiographic examination, independently from GH treatment.

Acknowledgments

We express our gratitude to all participating children and their parents for their enthusiastic participation in this study. The assistance of Ms. P.M.C.C. van Eekelen and Ms. M. Wevers is greatly appreciated. We are grateful for the work of Ms. J. P. Sluimer. We acknowledge Pfizer for their Independent Research Grant.

Address all correspondence and requests for reprints to: Roderick de Lind van Wijngaarden, Clinical Research Fellow, Dutch Growth Research Foundation, Erasmus University Medical Center/Sophia Children's Hospital, Westzeedijk 106, 3016 AH Rotterdam, The Netherlands. E-mail: r.delindvanwijngaarden@erasmusmc.nl or r.delind@kindengroei.nl.

Clinical trial no.: ISRCTN 49726762.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Cassidy SB, Schwartz S** 1998 Prader-Willi and Angelman syndromes. Disorders of genomic imprinting. Medicine (Baltimore) 77:140–151
2. **Festen DA, de Weerd AW, van den Bossche RA, Joosten K, Hoeve H, Hokken-Koelega AC** 2006 Sleep-related breathing disorders in prepubertal children with Prader-Willi syndrome and effects of growth hormone treatment. J Clin Endocrinol Metab 91:4911–4915
3. **Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F** 1993 Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics 91:398–402
4. **Goldstone AP** 2004 Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. Trends Endocrinol Metab 15:12–20
5. **Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB** 2001 The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. Pediatrics 108:E92
6. **McCandless SE, Cassidy SB** 2006 Diagnostic criteria for Prader-Willi syndrome. In: Butler MG, Lee PDK, Whitman BY, Association P-WS, eds. Management of Prader-Willi syndrome. 3rd ed. New York: Springer; 49–57
7. **Bittel DC, Butler MG** 2005 Prader-Willi syndrome: clinical genetics, cytogenetics and molecular biology. Expert Rev Mol Med 7:1–20
8. **State MW, Dykens EM** 2000 Genetics of childhood disorders: XV. Prader-Willi syndrome: genes, brain, and behavior. J Am Acad Child Adolesc Psychiatry 39:797–800
9. **Muscatelli F, Abrous DN, Massacrier A, Boccaccio I, Le Moal M, Cau P, Cremer H** 2000 Disruption of the mouse Necdin gene results in hypothalamic and behavioral alterations reminiscent of the human Prader-Willi syndrome. Hum Mol Genet 9:3101–3110
10. **Swaab DF** 1997 Prader-Willi syndrome and the hypothalamus. Acta Paediatr Suppl 423:50–54
11. **Swaab DF, Purba JS, Hofman MA** 1995 Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. J Clin Endocrinol Metab 80:573–579
12. **Cobb J** 1948 Outline for the study of scoliosis. In: Edwards JW, ed. Ann Arbor, Michigan: The American Academy of Orthopaedic Surgeons; 261–275
13. **de Lind van Wijngaarden RF, de Klerk LW, Festen DA, Hokken-Koelega AC** 2008 Scoliosis in Prader-Willi syndrome: prevalence, effects of age, gender, body mass index, lean body mass and genotype. Arch Dis Child 93:1012–1016
14. **Nagai T, Obata K, Ogata T, Murakami N, Katada Y, Yoshino A, Sakazume S, Tomita Y, Sakuta R, Niikawa N** 2006 Growth hormone therapy and scoliosis in patients with Prader-Willi syndrome. Am J Med Genet A 140:1623–1627
15. **Odent T, Accadbled F, Koureas G, Cournot M, Moine A, Diene G, Molinas C, Pinto G, Tauber M, Gomes B, de Gauzy JS, Glorion C** 2008 Scoliosis in patients with Prader-Willi syndrome. Pediatrics 122:499–503
16. **Diepstraten A, Van Linge B, Swierstra B** 2001 Afwijkingen van de wervelkolom. In: Kinderorthopedie. 2nd ed. Maarssen, The Netherlands: Elseviers gezondheidszorg 43–47
17. **Carrel AL, Allen DB** 2000 Effects of growth hormone on body composition and bone metabolism. Endocrine 12:163–172
18. **Carrel AL, Moerchen V, Myers SE, Bekx MT, Whitman BY, Allen DB** 2004 Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. J Pediatr 145:744–749
19. **Eiholzer U, L'Allemand D, Schlumpf M, Rousson V, Gasser T, Fusch C** 2004 Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome. J Pediatr 144:753–758
20. **Festen DA, Wevers M, de Weerd AW, van den Bossche RA, Duivenvoorden HJ, Otten BJ, Wit JM, Hokken-Koelega AC** 2007 Psychomotor development in infants with Prader-Willi syndrome and associations with sleep-related breathing disorders. Pediatr Res 62:221–224
21. **Ritzen EM, Lindgren AC, Hagenas L, Marcus C, Muller J, Blichfeldt S** 1999 Growth hormone treatment of patients with Prader-Willi syndrome. Swedish Growth Hormone Advisory Group. J Pediatr Endocrinol Metab 12(Suppl 1): 345–349
22. **Whitman B, Carrel A, Bekx T, Weber C, Allen D, Myers S** 2004 Growth hormone improves body composition and motor development in infants with Prader-Willi syndrome after six months. J Pediatr Endocrinol Metab 17:591–600
23. **Festen DA, de Lind van Wijngaarden R, van Eekelen M, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC** 2008 Randomized controlled growth hormone trial: effects on anthropometry, body composition, and body proportions in a large group of children with Prader-Willi syndrome. Clin Endocrinol (Oxf):443–451
24. **Burwell RG** 2003 Aetiology of idiopathic scoliosis: current concepts. Pediatr Rehabil 6:137–170
25. **Docquier PL, Mousny M, Jouret M, Bastin C, Rombouts JJ** 2004 Orthopaedic concerns in children with growth hormone therapy. Acta Orthop Belg 70: 299–305
26. **Wever DJ, Tonseth KA, Veldhuizen AG, Cool JC, van Horn JR** 2000 Curve progression and spinal growth in brace treated idiopathic scoliosis. Clin Orthop Relat Res 169–179
27. **Ahl T, Albertsson-Wikland K, Kalen R** 1988 Twenty-four-hour growth hormone profiles in pubertal girls with idiopathic scoliosis. Spine 13:139–142
28. **Skogland LB, Miller JA** 1980 Growth related hormones in idiopathic scoliosis. An endocrine basis for accelerated growth. Acta Orthop Scand 51:779–780
29. **Willner S, Nilsson KO, Kastrup K, Bergstrand CG** 1976 Growth hormone and somatomedin A in girls with adolescent idiopathic scoliosis. Acta Paediatr Scand 65:547–552
30. **Diene G, de Gauzy JS, Tauber M** 2008 Is scoliosis an issue for giving growth hormone to children with Prader-Willi syndrome? Arch Dis Child 93:1004–1006
31. **Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M** 2008 Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab 93:4183–4197
32. **Odent T, Accadbled F, Koureas G, Cournot M, Moine A, Diene G, Molinas C, Pinto G, Tauber M, Gomes B, de Gauzy JS, Glorion C** 2008 Scoliosis in patients with Prader-Willi Syndrome. Pediatrics 122:e499–e503
33. **Tanner JM, Whitehouse RH** 1976 Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 51:170–179
34. **Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM** 2000 Continuing positive secular growth change in The Netherlands 1955–1997. Pediatr Res 47:316–323
35. **Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP** 2000 Body index measurements in 1996–7 compared with 1980. Arch Dis Child 82:107–112
36. **Boot AM, Bouquet J, de Ridder MA, Krenning EP, de Muinck Keizer-Schrama SM** 1997 Determinants of body composition measured by dual-energy x-ray absorptiometry in Dutch children and adolescents. Am J Clin Nutr 66:232–238
37. **Boot AM, Nauta J, de Jong MC, Groothoff JW, Lilien MR, van Wijk JA, Kist-van Holthe JE, Hokken-Koelega AC, Pols HA, de Muinck Keizer-Schrama SM** 1998 Bone mineral density, bone metabolism and body composition of children with chronic renal failure, with and without growth hormone treatment. Clin Endocrinol (Oxf) 49:665–672
38. **Hokken-Koelega AC, Hackeng WH, Stijnen T, Wit JM, de Muinck Keizer-Schrama SM, Drop SL** 1990 Twenty-four-hour plasma growth hormone (GH) profiles, urinary GH excretion, and plasma insulin-like growth factor-I and -II levels in prepubertal children with chronic renal insufficiency and severe growth retardation. J Clin Endocrinol Metab 71:688–695
39. **Cohen J** 1988 Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates