

Late or Delayed Induced or Spontaneous Puberty in Girls with Turner Syndrome Treated with Growth Hormone Does Not Affect Final Height

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ABSTRACT

Although it has been well established that GH treatment increases final height (FH) in girls with Turner syndrome (TS), the optimal ages to start GH therapy and introduce estrogens for pubertal induction have not been defined. We evaluated retrospectively the influence of the age at onset of GH treatment and age at onset of puberty on FH of 186 adult TS women treated during childhood with GH. Puberty started spontaneously in 38 patients, and it was induced in 148 girls with ethinyl estradiol (mean \pm SD starting dose, 66 ± 32 ng/kg \cdot d). Patients with spontaneous or induced puberty were divided into quartiles on the basis of age at initiation of GH treatment (3–10, 10–12, 12–14, and 14–19 yr). FH was 151.7 ± 6.0 cm; there were no FH differences between patients with induced or spontaneous puberty, nor were there differences between the age quartiles. Puberty started earlier in the girls with spontaneous puberty than in those with induced puberty (12.4 ± 1.3 yr *vs.* 14.5 ± 1.9 yr; $P < 0.0001$). The age at onset of puberty was not related to FH. Pubertal growth was 15.4 ± 4.6 cm in the girls with spontaneous puberty and 8.6 ± 4.3 cm in the girls with induced puberty ($P < 0.0001$). We conclude that GH treatment results in a significant increase in FH in most TS girls. Under the conditions of GH treatment and induction of puberty that we have used, the age at start of GH treatment was not related to FH; in addition, late or delayed induced or spontaneous puberty did not affect FH.

ABBREVIATIONS

CMPH, Corrected midparental height; EE2, ethinyl estradiol; FH, final height; H-SDS, height SDS; SDS, sd score; TS, Turner syndrome.

The main characteristics of Turner syndrome (TS) are growth failure, with a mean final height (FH) of 144.3 ± 6.7 cm, and hypergonadotropic hypogonadism (1). Since the availability of recombinant human GH, girls with TS are offered treatment with GH to stimulate growth and to increase FH (2). Short-term results revealed a clear acceleration of height velocity when these patients were treated with supraphysiological doses of GH (3–5). FH data show widely divergent results with mean values of height gain between 3 and 16 cm (6–16), until near normalization of adult height (17, 18).

Because of ovarian dysgenesis, only about 20% of the girls with TS will develop puberty spontaneously (19), and induction of puberty with estrogens is required in the other girls. However, estrogens induce fusion of the epiphyses and are the limiting factor for longitudinal bone growth (20). Although some authors conclude that the addition of estrogens to GH therapy did not affect FH (8, 15), other studies suggest that the introduction of estrogens results in a decreased height gain with reduced FH (11, 13, 14), and it has been suggested that the addition of estrogens should be postponed as late as possible (11). On the other hand, postponing the introduction of estrogens too long can have adverse psychological consequences (21) and may result in a decreased bone mineralization (22, 23). Starting GH therapy at a relatively young age encompasses a longer period of estrogen-free GH treatment that could bring the patients' height into the normal range at the time of pubertal induction, permitting initiation of estrogen therapy at an age-appropriate time (12, 14, 18). However, the optimal ages at which treatment with GH and estrogens should be introduced are presently not clear. Current therapeutic guidelines recommend that growth promoting therapy with GH should be considered as soon as the height of a patient with TS has dropped below the fifth percentile of the normal female growth chart and may be started as early as 2 yr of age. Estrogen replacement therapy should be started no earlier than 12 yr and no later than 15 yr of age (24).

In the present publication, we report FH data of 186 young adult Belgian women with TS treated during childhood with GH. We evaluated retrospectively the effect of the age at start of GH treatment and the influence of initial height and parental height on FH. To study the effects of estrogens on FH, we compared the data from patients with induced puberty with those with spontaneous onset of puberty, and we evaluated the effect of the age at onset of puberty on pubertal growth and FH.

Patients and Methods

PATIENTS

From the database of the Belgian Study Group for Pediatric Endocrinology, patients fulfilling the following inclusion criteria were selected: 1) having cytogenetically confirmed TS; 2) being treated with daily injections of GH for at least 6 months with the intention to treat until FH; 3) having attained adult height, *i.e.* height velocity during the preceding year less than 1 cm or growth during

the last 6 months less than 0.5 cm. Patients with a known associated bone disease (25) were excluded. A total of 186 girls fulfilled all of the inclusion criteria. Karyotype distribution was: 91 (49%) 45,X; 21 (11%) 45,X/46,XX; 27 (15%) 45,X/46,Xi(Xq); 10 (5%) 45,X/46,XY; 10 (5%) 46,Xi(Xq); and 27 (15%) various other Turner karyotypes. The girls were born between March 1971 and January 1987. All patients and parents gave their informed consent for the GH and estrogen treatment.

GH TREATMENT

Treatment with GH started between December 1985 and December 1998 and was stopped between May 1989 and May 2001. Most of the patients in whom treatment was started between 1987 and 1992 participated in clinical trials of which short-term results have been published previously (4, 5, 26). From 1990, GH therapy was reimbursed for patients with TS in Belgium. In line with our psychological observations (26), GH treatment was usually started beyond the age of 6 yr. The median GH dose used at the initiation of treatment was 0.34 mg/kg·wk (mean \pm SD, 0.33 \pm 0.05 mg/kg·wk; range, 0.16–0.43 mg/kg·wk). The GH was administered as daily sc injections. The amount of injected GH was adapted every 3 months according to body weight to keep the dose as close as possible to the dose of 0.33 mg/kg·wk. The maximum GH dose was fixed at 2.7 mg/d.

PUBERTY

The patients were subdivided in two groups: group 1 consisted of patients without signs of spontaneous puberty (n = 148), and group 2 consisted of patients with spontaneous onset of puberty (n = 38). The karyotypes of the patients with spontaneous puberty were: 45,X (n = 10); 45,X/46,XX (n = 14); 45,X/47,XXX (n = 2); 45,X/46,Xi(Xq) (n = 4); 46,Xi(Xq) (n = 2); 45,X/46,Xr(X) (n = 2); 45,X/46,XX/46,Xr(X) (n = 1), and 46,Xdel(Xp) (n = 3). In the patients without spontaneous puberty, puberty was induced with low doses of ethinyl estradiol (EE2; starting dose, 66 \pm 32 ng/kg·d; range, 25–148 ng/kg·d) usually after at least 2 yr of GH therapy alone and at a minimum age of 11 yr. The dose of EE2 was increased every year to reach an adult dose (20 μ g/d) after 4 yr of treatment. Cyclic progestagen therapy was added during the third year of EE2 therapy. Of the patients with spontaneous puberty, seven already had Tanner (27) breast stage B3 or B4 at the start of GH treatment. Twenty-three experienced menarche spontaneously; in 15 girls, EE2 had to be added to complete puberty.

METHODS

Height was measured at baseline and subsequently every 3 months using a Harpenden stadiometer. FH was defined as the most recent available height after discontinuation of GH treatment and was evaluated about 1 yr after the stopping of GH treatment. Height data are expressed in centimeters and as SD scores (SDS) using the Tanner *et al.* (28) and the Lyon *et al.* references (29). Birth weight SDS was calculated using the Niklasson *et al.* reference (30). The onset of puberty was defined as the age at which EE2 therapy was initiated in the patients of group 1 and as the age when breast stage 2 (27) was observed for the first time in girls of group 2. Pubertal

growth was defined as the number of centimeters grown between the onset of puberty and FH. Corrected midparental height (CMPH) was calculated as: (father's height + mother's height)/2 – 6.5 cm) (Ref. 31).

The effect of treatment was evaluated by: 1) comparing FH of GH-treated patients with FH of historical untreated patients (19); and 2) by comparing the difference between CMPH and FH (*i.e.* the remaining height deficit).

STATISTICAL ANALYSIS

The patients were divided into quartiles on the basis of their ages at initiation of GH treatment: 3–10, 10–12, 12–14, and 14–19 yr. Results are expressed as mean \pm SD. Comparison between two groups was done by the unpaired *t* test. The Jonckheere-Terpstra nonparametric test was used to test for monotone trends across the baseline age groups. Simple linear regression analysis was performed to analyze the relationship between various baseline and treatment parameters, and FH and remaining height deficit (CMPH – FH).

Results

PATIENT CHARACTERISTICS AT START OF TREATMENT

Table 1 shows the baseline characteristics of the studied patients subdivided according to the occurrence of spontaneous puberty and according to the age quartile at the start of GH treatment. Chronological age at the start of GH treatment varied between 3.2 and 19.1 yr. Birth weight was -0.9 ± 1.2 SDS below the normal references and was significantly lower in the patients with induced puberty. CMPH was 161.6 ± 5.8 cm, which is nearly similar to the reference 50th percentile for adult women (162.2 ± 6.0 cm). CMPH was significantly lower in the girls with spontaneous puberty. Within each group, birth weight and CMPH were not different between the various age quartiles. The baseline Tanner height-SDS (H-SDS) decreased with age, whereas the Lyon H-SDS increased. The Tanner H-SDS as well as the Lyon H-SDS were higher in patients with spontaneous puberty.

PATIENT CHARACTERISTICS AT FH

Table 2 shows the endpoint data. Treatment with GH was stopped at the mean age of 16.8 ± 1.7 yr after a treatment period of 5.2 ± 2.6 yr. The GH treatment was stopped earlier in the girls with spontaneous puberty, who were treated for a shorter period of time. In both groups the age at stop of GH treatment increased, whereas the duration of GH treatment period decreased along the baseline age groups. Height at the stop of GH treatment was 151.0 ± 6.1 cm. FH, measured about 1 yr later, was 151.7 ± 6.0 cm. This is 8.3 cm higher than the adult height observed in untreated Belgian women with TS (143.4 ± 5.6 cm; $P < 0.0001$). Girls with spontaneous puberty reached their

FH about 1.5 yr earlier than girls with induced puberty. A total of 121 patients (65%) reached a FH of at least 150 cm. Expressed as SDS, FH was -1.75 ± 1.00 Tanner H-SDS and $+1.32 \pm 0.90$ Lyon H-SDS. There were no differences in FH between patients with or without spontaneous puberty or between the baseline age groups.

Table 1. Baseline characteristics by age quartiles at onset of GH therapy (mean \pm sd).

Quartile	No. (45,X)	Age (yr)	BW (SDS)	CMPH (cm)	Height (cm)	Height (Tanner SDS)	Height (Lyon SDS)
Group 1 (induced puberty)							
1	37 (21)	7.1 \pm 1.9	-1.01 \pm 1.22	161.0 \pm 5.9	106.3 \pm 9.2	-2.38 \pm 0.85	0.00 \pm 0.87
2	37 (21)	10.7 \pm 0.7	-1.07 \pm 1.36	161.4 \pm 6.4	123.1 \pm 6.3	-2.62 \pm 0.81	0.21 \pm 0.98
3	37 (22)	13.0 \pm 0.6	-1.39 \pm 1.12	162.2 \pm 4.6	133.1 \pm 4.8	-3.23 \pm 0.83	0.49 \pm 0.79
4	37 (17)	15.6 \pm 1.2	-1.11 \pm 1.47	163.6 \pm 5.9	139.2 \pm 6.9	-3.68 \pm 1.11	0.33 \pm 1.03
P			0.44	0.07	<0.0001	<0.0001	0.02
Total	148	11.6 \pm 3.4	-1.14 \pm 1.30	162.1 \pm 5.7	125.4 \pm 14.3	-2.97 \pm 1.03	0.26 \pm 0.93
Group 2 (spontaneous puberty)							
1	9 (3)	6.8 \pm 2.2	-0.46 \pm 1.75	157.3 \pm 5.7	104.9 \pm 11.6	-2.35 \pm 0.79	0.01 \pm 0.83
2	10 (3)	11.3 \pm 0.8	-0.75 \pm 1.74	161.8 \pm 5.9	129.6 \pm 7.4	-2.24 \pm 0.69	0.93 \pm 0.98
3	9 (1) ^a	13.3 \pm 0.3	-0.53 \pm 1.24	160.5 \pm 5.5	139.2 \pm 6.2	-2.60 \pm 0.79	1.34 \pm 0.90
4	10 (3) ^a	14.2 \pm 0.6	-0.77 \pm 1.49	160.3 \pm 5.7	141.4 \pm 7.0	-2.78 \pm 1.18	1.43 \pm 1.20
P			0.98	0.47	<0.0001	0.12	0.01
Total	38	11.5 \pm 3.1	-0.63 \pm 1.51	160.0 \pm 5.9	129.1 \pm 16.4	-2.50 \pm 0.93	0.91 \pm 1.1
Induced vs. spontaneous puberty (P)		0.81	0.04	0.047	0.17	<0.02	<0.0005

BW, Birth weight.

^a Respectively 3 and 5 patients of these quartiles already had breast stage B3 or B4 at the start of GH treatment.

The remaining height deficit (CMPH – FH) was 9.8 ± 6.4 cm, which is 6.5 cm less than in untreated women with TS (Ref. 19) (16.3 ± 4.7 cm; $P < 0.0001$). There was, however, a large interindividual variability, with 13 girls (7%) exceeding the CMPH and 28 girls (16%) attaining a FH greater than 16.3 cm below CMPH. We did not observe any significant differences between patients with induced or spontaneous puberty or between the various age groups.

PATIENT CHARACTERISTICS AT ONSET OF PUBERTY AND MENARCHE AND PUBERTAL GROWTH DATA

Table 3 shows the puberty-related data. Puberty started earlier in the girls with spontaneous puberty than in those with induced puberty, but the onset of puberty was in both groups later than in girls without TS [50th percentile, 10.9 yr (Ref. 32)]. In 94 girls (63%) with induced puberty, the induction of puberty was initiated beyond the age of 13.5 yr, the 95th age percentile for healthy

girls. In the two groups, puberty started earlier when GH treatment was started earlier. Menarche occurred about 1.9 ± 1.0 yr after the onset of puberty and was 3 yr later in girls with induced puberty and 1 yr later in girls with spontaneous puberty than in girls without TS [50th percentile, 13.15 yr (Ref. 32)].

Table 2. Endline characteristics by age quartiles at onset of GH therapy (mean \pm sd).

Quartile	Age at stop GH (yr)	Duration of GH therapy (yr)	Height at GH stop (cm)	Age at FH (yr)	FH (cm)	FH (Tanner SDS)	FH (Lyon SDS)	CMPH – FH (cm)
Group 1 (induced puberty)								
1	15.9 \pm 1.1	8.9 \pm 1.7	151.0 \pm 5.2	16.9 \pm 1.3	151.6 \pm 5.3	-1.77 \pm 0.88	1.29 \pm 0.78	9.2 \pm 6.5
2	16.6 \pm 1.2	5.9 \pm 1.3	151.3 \pm 6.3	17.8 \pm 1.2	152.1 \pm 6.3	-1.68 \pm 1.05	1.38 \pm 0.94	9.0 \pm 6.3
3	17.1 \pm 1.0	4.1 \pm 1.0	151.3 \pm 6.0	18.3 \pm 1.9	152.1 \pm 5.7	-1.69 \pm 0.95	1.37 \pm 0.85	10.2 \pm 4.8
4	18.8 \pm 1.4	3.2 \pm 1.4	150.8 \pm 7.0	20.0 \pm 1.5	151.6 \pm 6.9	-1.77 \pm 1.14	1.29 \pm 1.02	11.9 \pm 6.1
P	< 0.0001	< 0.0001	0.720	< 0.0001	0.863	0.547	0.547	0.052
Total	17.1 \pm 1.6	5.5 \pm 2.6	151.1 \pm 6.1	18.3 \pm 1.9	151.8 \pm 6.0	-1.73 \pm 1.00	1.33 \pm 0.90	10.2 \pm 6.1
Group 2 (spontaneous puberty)								
1	14.5 \pm 1.3	7.8 \pm 1.2	150.5 \pm 7.1	15.3 \pm 1.6	151.1 \pm 7.0	-1.85 \pm 1.17	1.22 \pm 1.05	6.2 \pm 6.8
2	15.3 \pm 1.1	4.0 \pm 1.2	151.3 \pm 3.8	16.6 \pm 2.0	151.8 \pm 3.6	-1.73 \pm 0.60	1.33 \pm 0.54	10.0 \pm 6.1
3	15.7 \pm 1.3	2.5 \pm 1.3	149.9 \pm 8.2	16.6 \pm 1.7	150.9 \pm 8.5	-1.89 \pm 1.42	1.19 \pm 1.27	9.0 \pm 7.2
4	16.8 \pm 1.7	2.7 \pm 1.6	151.1 \pm 6.1	17.8 \pm 1.8	151.4 \pm 6.4	-1.80 \pm 1.07	1.27 \pm 0.96	9.0 \pm 7.2
P	< 0.0006	< 0.0001	0.896	0.08	0.876	0.774	0.876	0.735
Total	15.6 \pm 1.5	4.2 \pm 2.5	150.7 \pm 6.2	16.6 \pm 1.9	151.3 \pm 6.3	-1.82 \pm 1.05	1.25 \pm 0.94	8.6 \pm 7.6
Induced vs. spontaneous puberty (P)	< 0.0001	0.0047	0.72	< 0.0001	0.63	0.63	0.63	0.24

The prepubertal (estrogen-free) period of GH treatment was longer in the girls with induced puberty. In both groups, the duration of the estrogen-free treatment period decreased with ongoing age at the start of GH therapy. Tanner H-SDS at the onset of puberty was 0.62 ± 0.56 SDS and 0.62 ± 0.68 SDS above H-SDS at the start of GH treatment in the girls with induced puberty and in those with spontaneous puberty, respectively. In both groups, the prepubertal increase in H-SDS was most pronounced in the girls of the first and fourth quartiles. The girls of the first quartile reached a mean H-SDS at the start of puberty within the lower normal range.

The duration of pubertal growth phase was 2.6 ± 1.4 yr and was not different between girls with induced or spontaneous puberty. The duration of the pubertal growth period decreased with ongoing age. Girls with spontaneous puberty grew 15.4 ± 4.6 cm during puberty, whereas the patients with induced puberty grew only 8.6 ± 4.3 cm ($P < 0.0001$) during puberty. In the girls with induced puberty, pubertal growth decreased significantly with ongoing age. Compared with the Tanner H-SDS at the start of puberty, the H-SDS at adult height was 0.62 ± 0.70 SDS greater in the girls with induced puberty and 0.28 ± 1.07 SDS in the girls with spontaneous puberty. The changes

in H-SDS during puberty increased with ongoing age at the start of GH treatment, and although the girls in the first quartiles had a good pubertal growth in centimeters, their H-SDS even decreased slightly.

Table 3. Characteristics of puberty and pubertal growth (mean \pm sd).

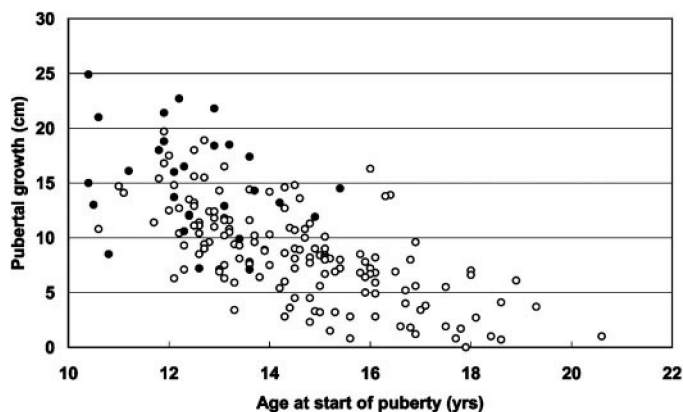
Quartile	Onset of puberty (yr)	Age at menarche (yr)	E-free GH therapy (yr)	Height at start puberty (cm)	Height at start puberty (Tanner SDS)	Prepubertal change in H-SDS	GH + E therapy (yr)	Pubertal growth (cm)	Pubertal change in H-SDS
Group 1 (induced puberty)									
1	12.7 \pm 1.0	14.8 \pm 1.3 (32)	5.6 \pm 1.9	141.2 \pm 6.1	-1.68 \pm 1.03	0.70 \pm 0.48	3.2 \pm 1.1	10.3 \pm 3.7	-0.08 \pm 0.54
2	14.0 \pm 1.2	15.6 \pm 1.1(34)	2.7 \pm 1.0	141.5 \pm 4.8	-2.37 \pm 1.00	0.24 \pm 0.49	3.1 \pm 1.1	10.8 \pm 4.1	0.70 \pm 0.57
3	14.8 \pm 0.8	16.2 \pm 1.0 (32)	1.8 \pm 0.6	144.1 \pm 4.3	-2.72 \pm 0.77	0.50 \pm 0.44	2.3 \pm 1.0	8.0 \pm 3.5	1.03 \pm 0.53
4	17.1 \pm 1.2	18.7 \pm 1.3 (30)	1.5 \pm 0.7	146.2 \pm 6.4	-2.65 \pm 1.07	1.03 \pm 0.55	1.7 \pm 1.2	5.3 \pm 3.8	0.84 \pm 0.64
<i>P</i>	< 0.0001	< 0.0001	< 0.0001	0.0033	< 0.0001	0.0048	< 0.0001	< 0.0001	< 0.0001
Total	14.5 \pm 1.9	16.3 \pm 1.8	2.9 \pm 2.0	143.3 \pm 5.8	-2.35 \pm 1.05	0.62 \pm 0.56	2.6 \pm 1.3	8.6 \pm 4.3	0.62 \pm 0.70
Group 2 (spontaneous puberty)									
1	11.5 \pm 1.0	12.8 \pm 1.4	4.0 \pm 2.2	136.8 \pm 5.5	-1.28 \pm 0.99	1.25 \pm 0.78	3.9 \pm 1.9	13.9 \pm 4.0	-0.41 \pm 0.88
2	11.9 \pm 0.8	14.7 \pm 2.3	0.6 \pm 0.5	133.9 \pm 5.3	-1.97 \pm 0.69	0.38 \pm 0.43	3.3 \pm 1.0	18.3 \pm 5.4	0.00 \pm 0.81
3	13.0 \pm 0.8 ^a	14.3 \pm 1.5	0.2 \pm 0.3	138.1 \pm 6.7 ^a	-2.44 \pm 0.85 ^a	0.26 \pm 0.32 ^a	2.3 \pm 1.2	15.1 \pm 5.0	0.92 \pm 1.11
4	14.2 \pm 0.9 ^a	15.0 \pm 1.7	0.2 \pm 0.4	142.2 \pm 6.1 ^a	-2.94 \pm 1.27 ^a	0.53 \pm 0.76 ^a	2.5 \pm 1.3	13.6 \pm 2.8	1.03 \pm 1.13
<i>P</i>	< 0.0001	0.012	< 0.0001	0.065	0.0037	0.011	0.02	0.89	0.004
Total	12.4 \pm 1.3 ^a	14.2 \pm 1.9	1.2 \pm 1.9	137.2 \pm 6.1 ^a	-2.05 \pm 1.05 ^a	0.62 \pm 0.68 ^a	3.0 \pm 1.5	15.4 \pm 4.6	0.28 \pm 1.07
Induced vs. spontaneous puberty (<i>P</i>)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.16	1.00	0.10	< 0.0001	0.0293

E, Estrogen.

^a These results are only for the patients in whom puberty did not start before the onset of GH treatment (quartile 3, n = 6; quartile 4, n = 5).

In the girls with induced puberty as well as in those with spontaneous puberty, the age at start of puberty was positively related to the age at the start of GH treatment ($r = 0.85$, $P < 0.0001$; and $r = 0.74$, $P < 0.0001$, respectively). Pubertal growth in centimeters was inversely related to the age at start of GH treatment ($r = -0.45$; $P < 0.0001$) and to the age at start of puberty ($r = -0.67$; $P < 0.0001$) in the girls with induced puberty, whereas no such relationship could be demonstrated in the girls with spontaneous puberty (**Fig. 1**).

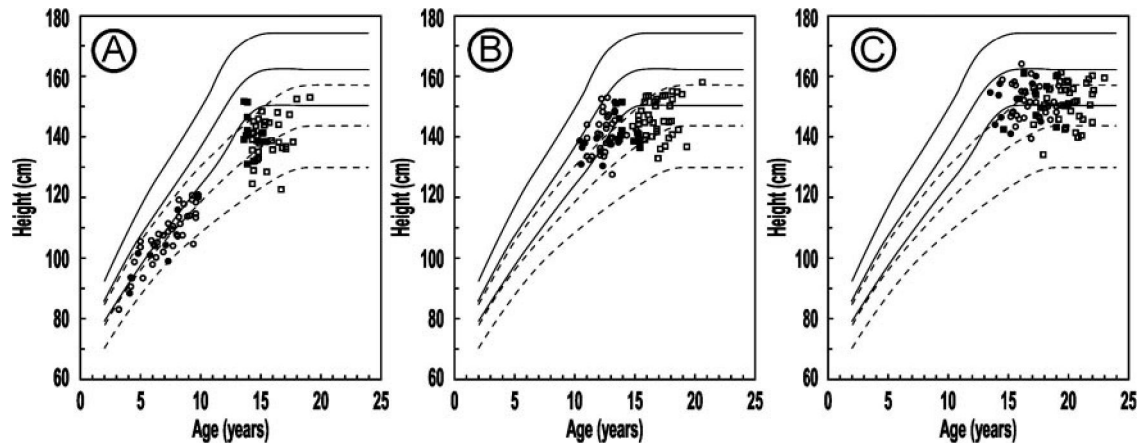
Fig. 1. Pubertal growth as a function of the age at start of puberty. E, Patients with induced puberty; F, patients with spontaneous puberty.



SUMMARY OF GROWTH DURING GH TREATMENT

Figure 2 summarizes the growth data of the patients with induced and spontaneous puberty of the first and fourth quartiles at the start of GH treatment (**Fig. 2A**), at the start of puberty (**Fig. 2B**), and at FH (**Fig. 2C**). At the start of treatment, nearly all girls had their height within the Turner references. Eleven girls with induced puberty and two with spontaneous puberty belonging to the first quartile group had their height within the lower normal population references, whereas only two patients with spontaneous puberty and two with induced puberty of quartile 4 had their height within the normal range. At the start of puberty, 20 patients with induced puberty and six patients with spontaneous puberty belonging to quartile 1 had their height within the lower normal reference range, whereas only five girls with induced puberty and three with spontaneous puberty of the fourth quartile had their height above the -2 SD line of the normal population. Moreover, puberty was induced in most of the quartile 1 patients before the age of 13.5 yr, the 95th percentile of healthy girls. Girls of the first quartile reached their FH earlier than girls of the fourth quartile, but adult height was similar for the patients of quartiles 1 and 4, as well as for the patients with induced or spontaneous puberty. These figures clearly show that: 1) at the onset of GH therapy, quartile 1 patients are less small in comparison to their peers than quartile 4 patients; 2) most quartile 1 patients reach a low normal height at the onset of puberty, which started at a late to delayed age; and 3) although treatment was started late, quartile 4 patients reached an adult height similar to quartile 1 patients.

Fig. 2. Height at the start of GH treatment (A), at the onset of puberty (B), and at FH (C) of the TS girls belonging to quartiles 1 (circles) and 4 (squares). Open symbols represent patients with induced puberty, and closed symbols represent patients with spontaneous puberty. Reference curves are given for healthy girls (-2, 0, and +2 sd lines) and untreated girls with TS (-2, 0, and +2 sd lines).



FACTORS RELATED TO FH AND REMAINING HEIGHT DEFICIT

The results of the linear regression analysis are shown in **Table 4**. Lyon H-SDS at the start of treatment and CMPH were the baseline variables most strongly related to the outcome parameters: the taller the girl at the start of GH treatment, the taller was her FH and the smaller the height deficit; the taller the parents, the taller FH will be, but the remaining height deficit remains larger. Lyon H-SDS at the start of puberty and pubertal growth were positively related to FH and inversely related to the remaining height deficit. The age at the start of GH treatment and at the start of puberty were not related to FH and were only weakly related to the remaining height deficit in the patients with induced puberty. The total duration of GH treatment and the estrogen-free GH treatment period were not related to FH. The duration of the GH plus estrogen treatment period was related positively to FH and inversely to the remaining height deficit.

Discussion

The present analysis confirms that girls with TS treated with GH in a dose of 0.33 mg/kg · wk have a significant increase in adult height compared with untreated TS women. The most important determinants of FH are the height at start of GH treatment and parental height. We did not observe any influence of the age at onset of GH treatment or the age of introduction of estrogens on FH.

To evaluate the effects of GH treatment, we looked at FH in centimeters, in comparison to a historical control group, and to the remaining height deficit calculated as the difference between corrected midparental height and FH, which might compensate for secular trends in growth. In contrast to most other reports on FH in TS, we did not evaluate the so-called height gain according to the projected FH method of Lyon *et al.* (29), which is usually calculated as the difference between final H-SDS and the initial H-SDS using the Lyon or other TS references. Although the Lyon

references are useful to compare the height of TS girls with other TS girls, these references underestimate the child's height at a young age and overestimate the height at an older age (Ref. 33; also, Massa, G., S. Verlinde, and C. Heinrichs, submitted for publication), which will contribute to the conclusion that young TS girls treated with GH have a larger height gain than older girls with TS. Moreover, what really counts for the patients and their parents is height in absolute centimeters and height in comparison to parental height, not the number of centimeters that they were supposed to gain with growth-promoting therapy.

Table 4. Results of simple linear regression analysis (Pearson correlation coefficient) between baseline and treatment variables and outcome parameters.

	FH (cm)		CMPH – FH (cm)	
	Group 1	Group 2	Group 1	Group 2
Birth weight-SDS	0.11	0.41 ^a	0.02	-0.32 ^a
GH dose	0.00	0.13	-0.02	-0.15
Age at start GH treatment	-0.08	0.07	0.17 ^a	-0.02
Lyon H-SDS at start GH treatment	0.57 ^d	0.48 ^c	-0.27 ^b	-0.17
Corrected midparental height	0.47 ^d	0.24	0.47 ^d	0.59 ^c
Age start puberty	-0.12	-0.19	0.17 ^a	0.16
Lyon H-SDS at start puberty	0.80 ^d	0.59 ^b	-0.48 ^d	-0.23
Pubertal growth	0.41	0.45 ^a	-0.34	-0.47 ^a
Duration of GH treatment	0.14	0.05	-0.25 ^b	-0.20
Duration of E-free GH treatment	0.01	-0.20	-0.10	0.03
Duration of (GH + E) treatment	0.26 ^b	0.35	-0.32 ^c	-0.39 ^a

E, Estrogen.

^a $P < 0.05$; ^b $P < 0.005$; ^c $P < 0.0005$; ^d $P < 0.0001$.

In Belgium, mean FH in the young adult TS women treated during childhood with GH was 151.7 ± 6.0 cm, which is about 8.3 cm taller than the FH we reported in untreated Belgian Turner women (19). Sixty-five percent of the girls reached an adult height greater than 150 cm. Our results are in line with the most recent data from the literature using similar GH doses of 0.33 mg/kg·wk: mean FH varies between 146.8 and 152.2 cm (6–8, 12, 14, 15). Comparing FH to CMPH revealed a remaining height deficit of 9.8 ± 6.4 cm, which is 6.5 cm less than in untreated women with TS. This result is better than reported by Hochberg and Zadik (6), who reported a remaining height deficit of 16.0 ± 4.6 cm, 4.7 cm less than an untreated control group. Taken together, our data and those from the literature clearly show an incontestably significant effect of GH treatment on FH of girls with TS.

There is, however, a large interindividual variability in the response to GH therapy. In line with the results of most other reports (2, 6, 7, 11), we found that height at the start of treatment is the most important variable related to FH. Height at the start of treatment was related to parental height, and FH was also strongly related to parental height (2). Hence, TS girls who are short on the TS references at the start of GH treatment will end up with a smaller FH than tall TS girls. These

findings stress the importance of genetic factors influencing growth. Indeed, in addition to having TS with haploinsufficiency of the *SHOX* gene (34), these girls may suffer from familial short stature or intrauterine growth retardation, whatever the cause may be. The question arises whether treating these girls with higher doses of GH, as used in children with intrauterine growth retardation (35), would improve their adult height. Indeed, the best FH results, with even normalization of height, were reported in the Dutch study using higher doses of GH (18). The large interindividual variability in the response to GH treatment also stresses the need for individualized GH treatment in girls with TS to optimize FH results (24, 36).

Interestingly, in our study we did not find any difference in FH between girls with induced puberty and those with spontaneous puberty, and we did not observe any relationship between the age at onset of puberty and FH. Thirty-eight girls (20%) showed signs of spontaneous puberty beginning at a mean age of 12.4 ± 1.3 yr, and 23 of them experienced menarche spontaneously. FH in the girls with spontaneous ovarian activity was 151.3 ± 6.3 cm, whereas girls with induced puberty reached an adult height of 151.8 ± 6.0 cm. This finding is in line with the observations of Reiter *et al.* (12) who also did not find any difference in FH between girls with spontaneous puberty and those with induced puberty (148.9 ± 5.8 vs. 149.9 ± 5.9 cm). In the latter study, the mean age at onset of spontaneous puberty was 13.0 ± 1.9 yr. Contrasting are the data reported by Cacciari *et al.* (11) who observed a FH of 143.0 ± 5.3 cm in 10 TS girls with spontaneous menarche, whereas girls without ovarian activity reached a FH of 148.9 ± 5.5 cm. However, they did not mention at what age spontaneous puberty and menarche occurred. Schweizer *et al.* (7) also observed that FH did not exceed the initially projected adult height in three TS girls who had spontaneous puberty before the age of 12 yr. The fact that we and Reiter *et al.* (12) did not observe any difference in FH between girls with spontaneous and induced puberty may be due to the relative late onset of puberty in our TS girls with spontaneous puberty. Obviously, spontaneous puberty occurring at a young age in TS girls might compromise spontaneous or stimulated growth, and some authors advocate the use of GnRH analogs in these girls to maximize height gain (37).

There are, however, some important differences in pubertal development and growth between the girls with spontaneous and induced puberty. Most of the girls with spontaneous puberty started their puberty in the upper normal age range (10.9–13.5 yr; Ref. 32). In contrast, in the girls with induced puberty estrogen therapy was initiated beyond the normal median age of pubertal onset, and in 63% beyond the 90th age percentile. Only in the girls starting GH treatment relatively early was puberty induced at a late normal time. This finding confirms the observation of Reiter *et al.* (12) that early initiation of GH treatment allows age-appropriate estrogen use in TS girls. Indeed, we may not forget that in addition to their short stature, untreated TS girls often suffer for a longer time from their hypogonadism and absence of sexual development accentuating the differences with their peers.

Postponing the introduction of estrogens has been advocated to benefit maximally from the growth promoting effect of GH (11, 14). In our patients with induced puberty, starting puberty with low-dose estrogens at a late to delayed age, after about 2 yr of GH treatment alone, we could not find any influence of estrogens on FH. In line with our 3-yr observations (38) in which we reported

that spontaneous puberty during GH treatment has an additive effect on height velocity, we now observed that total pubertal growth in girls with spontaneous puberty was superior to that observed in the girls with induced puberty. Although the duration of the period of GH therapy combined with endogenous or exogenous estrogens was similar for girls with induced and spontaneous puberty (2.6 ± 1.3 yr vs. 3.0 ± 1.5 yr), and comparable to normal girls, growth during puberty was only 8.6 ± 4.3 cm in girls with induced puberty, whereas girls with spontaneous puberty grew 15.4 ± 4.6 cm. This difference is for a large part due to difference in the age at onset of puberty, because we clearly showed that pubertal growth is inversely related to the age at the start of puberty. Girls in whom puberty is induced later have a longer prepubertal growth phase, apparently balancing for the lower pubertal growth. A similar relationship has been observed in normal girls and in hypopituitary girls with induced or spontaneous puberty (39). However, the changes in Tanner H-SDS, reflecting catch-up growth, were very different among the age quartiles because height was compared with the height of healthy girls. In the patients of quartile 1, H-SDS slightly decreased during puberty showing that they did not show any further catch-up growth, whereas in the patients of quartile 4, H-SDS increased reflecting further catch-up in comparison to their age-mates.

Comparing groups of TS girls starting GH treatment at different ages, we did not find any difference in FH or in the remaining height deficit. Hence, it may be concluded that the age at the start of GH treatment is not important in girls with TS as long as FH is considered. However, although the baseline variables between the age quartiles were similar, the groups may not be strictly comparable because of a bias in the recruitment of the patients. Most of the oldest patients were included in the first clinical trials on the use of GH in TS, and they have grown for a longer time when GH treatment was not available. Anyway, our data indicate that TS girls who started their GH treatment early can reach a height in the lower normal range at the start of induction of puberty and, although they did not show any further catch-up growth, they remained at their attained percentile during pubertal induction. Hence, the main benefit of starting relatively early GH treatment is normalization of height during childhood, enabling induction of puberty at a normal age. Moreover, early initiation of GH treatment will prevent further height loss of TS girls compared with their healthy peers, and might reduce the psychological burden of short stature (26). In addition, timely initiation of GH treatment allows age-appropriate estrogen use and might reduce the psychological burden of hypogonadism. Because the perception of short stature is not yet problematic in TS girls younger than 6 yr of age, although the acceptance of daily injections might be a problem in this age group (26), more data are needed to delineate the optimal age to start GH treatment, taking into account the auxological as well as psychosocial status of each individual girl and her parents.

In summary, our data confirm that GH treatment in a dosage of 0.33 mg/kg·wk results in a significant increase in FH in most girls with TS. The major determinant of FH is the height at the start of treatment, which is related to parental height. Under the conditions of GH treatment and induction of puberty we have used in Belgium, the age at the start of GH treatment was not related to FH, and late or delayed puberty, spontaneous or induced, did not seem to influence FH. Further

prospective studies evaluating the influence of the age at start of GH treatment and the age at induction of puberty are indicated to confirm the results obtained from our retrospective analysis.

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