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Adult Height and Pubertal Growth in Turner Syndrome after Treatment with Recombinant Growth Hormone

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Objective: The objective of this study was to evaluate factors affecting adult height (AH) in patients with Turner syndrome treated with GH.

Design: The study design was a population-based cohort study.

Setting: The setting was The StaTur Study, a register of patients treated in France between 1986 and 1997, followed for a mean of 9.3 yr.

Patients: We followed 704 of the 891 eligible patients (79%) to AH.

Intervention: GH (0.8 ± 0.2 IU/kg·wk; 0.26 ± 0.06 mg/kg·wk; mean ± SD) was administered for 5.0 ± 2.2 yr. Puberty was classified as spontaneous (10%), spontaneous with secondary estrogens (13%), or induced (77%). Estrogen treatment was initiated at 15.0 ± 1.9 yr of age in those with induced puberty.

Main Outcome Measure: The main outcome measure was multivariate analysis of AH after grouping potential predictors.

Results: The mean AH was 149.9 ± 6.1 cm, 8.5 cm above projected height. The model explained 90% of the variance, with major effects of age at initiation and duration of treatment. Other factors included birth length, target height, bone age delay and weight at initiation of treatment, age at pubertal onset, GH dose, and number of injections per week. Age at introduction of estrogens was not a predictor, and the use of percutaneous *vs.* oral estrogens was associated with greater height (+2.1 cm; 95% confidence interval, 1.00–3.25).

Conclusions: Our results support the early initiation of GH treatment and induction of puberty at a physiological age to achieve optimal AH. They suggest that GH should be injected daily, and percutaneous estrogens used. These results should be considered in the context of the lack of demonstrable influence of AH on psycho-social outcomes, uncertainties regarding long-term safety, and treatment cost. **(*J Clin Endocrinol Metab* 90: 5197–5204, 2005)**

TURNER SYNDROME, FIRST described in 1938 (1), is a common chromosomal disorder, affecting approximately one in every 2500 liveborn females. It results from the partial or total absence of one of the X-chromosomes (2). Short stature is a common feature of Turner syndrome, and adult patients have a mean height approximately 20 cm lower than that of unaffected women in the same ethnic group (2–4). Short stature results partly from haploinsufficiency of the SHOX gene on the distal part of the short arm of chromosome-X; the GH/IGF-I axis is normal in Turner syndrome (2).

Treatment with recombinant human GH has been offered to most affected children since the early 1990s and is now considered standard (5). This treatment has been shown to increase growth rate in the short term (6). Comparisons of adult heights (AHs) with pretreatment predicted heights based on disease-specific normative data (3, 7) have shown variable outcomes, ranging from no effect (8–10) to a mean increase of up to 16.9 cm (11–19). This variability may be accounted for by several factors, including age at GH initiation, ethnic origin, GH dose, and pubertal management. Most AH reports have been based on clinical trials, for which generalization may not be valid (11, 13, 14, 17, 18), whereas others have been based on large postmarketing databases with potential biases (particularly completion bias, where those who stay in the study until AH might have better outcome than those who stop treatment and are lost to follow-up) (12, 16). More recently, the Canadian randomized trial has confirmed that GH treatment increased AH in Turner syndrome (20).

Gonadal dysgenesis is another key feature of Turner syndrome. Spontaneous pubertal development occurs in only about 20% of patients, with 2–5% experiencing spontaneous menarche (21), and the vast majority of patients with Turner syndrome requiring treatment with estrogens and progestin to achieve adequate pubertal development (2). Estrogens have been shown to be involved in epiphyseal fusion (22). This has called into question the timing and means of sex steroid treatment in adolescents with Turner syndrome, with

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Abbreviations: AH, Adult height; SDS, SD score.

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some experts advocating early pubertal induction and others late pubertal induction, based on psycho-social or auxological issues (14, 23, 24).

In this study we evaluated the determinants of AH in the population-based register of all young women with Turner syndrome treated with GH in France. Given the controversies surrounding pubertal induction, we took particular care to analyze the effects of this factor.

Patients and Methods

Patients

The StaTur cohort includes all patients with a diagnosis of Turner syndrome based on karyotype analysis who were treated with GH in France during the study period (1986–1997) and were obligatorily registered in the Association France-Hypophyse database (25). We then selected patients over the age of 18 yr on March 1, 2001 (Fig. 1).

Data collected

Data were collected at start of treatment and yearly thereafter on a prospective ongoing basis, up to 1997. Additional data were collected retrospectively in 2001. All data were collected using standardized data collection forms. Data relating to growth, karyotype, dysmorphic features, and cardiac and renal malformations associated with Turner syndrome were collected before treatment. Pediatric endocrinologists then recorded age, height, weight, bone age, associated morbidity, pubertal stage, GH dose, frequency of injections, and associated treatments at follow-up visits (every 3–6 months) (25). Height and weight were expressed as SD scores (SDS), based on the normative general population (25) and Turner syndrome data (7). Projected AH was calculated from Turner syndrome data (7). In 2001, we prospectively collected follow-up data from pediatric endocrinologists. We considered that AH had been attained if growth rate was 1 cm/yr or less (n = 262) or if bone age was 16 yr or greater (99.6% of AH; n = 541) (26).

GH treatment

Treatment was generally initiated at diagnosis of Turner syndrome. However, for the older patients, treatment was initiated when GH became widely available, in the early 1990s. Patients were eligible to receive GH if their bone age was 12 yr or less. Association France Hypophyse decided annually whether the treatment should be continued. Criteria for discontinuation of treatment were growth rate less than 3 cm/yr or bone age of 13 yr or more, defining treatment completion.

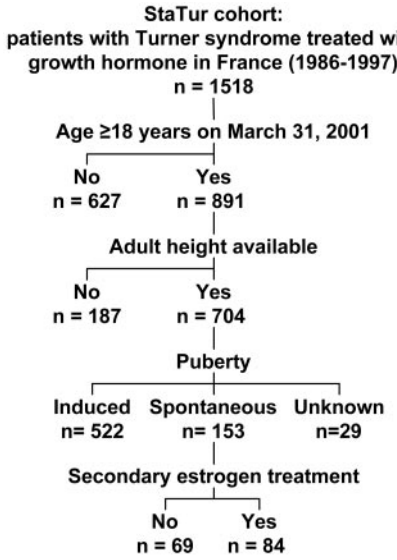

FIG. 1. Distribution of the patients.

Puberty and pubertal growth

Age at pubertal onset was defined as the age at durable B2 stage (27) in patients with spontaneous development or at initiation of estrogen therapy in patients with induced puberty. Pubertal growth was defined as growth occurring between the onset of puberty and AH and was split into growth with and without GH treatment.

Decisions to administer sex steroid treatment at puberty and the management of this treatment were dealt with on an individual basis. Patients were subdivided into patients with and without spontaneous pubertal breast development. All patients with induced puberty and roughly half of those with spontaneous puberty were treated with estrogens, defining three classes of pubertal development: spontaneous puberty/no estrogen, spontaneous puberty/estrogen, and induced puberty/estrogen. Estrogen treatments were classified into four types: oral ethinyl estradiol, oral estradiol, percutaneous estradiol, and estrogen-progestin combinations. Typical initial doses for estrogen preparations were as follows: ethinyl estradiol, 1–5 μg/d; estradiol, 0.5 mg/d; and percutaneous estradiol, one quarter of a 25 μg/d patch or one quarter of the daily replacement dose of gel. Because progestin treatments are prescribed when estrogen doses have reached adult replacement levels or when menstrual bleeding appears, we used the delay between the initiation of estrogen and the initiation of progestin treatments as a surrogate for estrogen dose increment, classifying this variable into three classes: less than 1 yr, 1–2 yr, or more than 2 yr.

Statistical analysis

Results are expressed as the mean ± SDS for height and weight for age, sex, or gestational age, and target heights were calculated (28). A model for AH (centimeters) prediction was constructed in several stages, as previously described (29, 30). The potential predictors were subgrouped: those accounting for regression toward the mean, those describing genetic growth potential, those describing the child at baseline, and those describing GH and associated treatments. The variables in each group were tested as predictors of outcome, after adjustment for variables identified at previous stages, leading to the establishment of a final model. The main outcome response, AH (centimeters), was approximately normally distributed. GH dose was not normally distributed, and its effect was analyzed after log transformation. Because all models were adjusted for baseline height (centimeters), they describe both AH gain and AH itself (centimeters). We analyzed the effect of age at induction of puberty by constructing a second model, using only patients with induced puberty. Calculations were performed with SAS software (SAS Institute, Inc., Cary, NC) (31).

Results

Patient characteristics at baseline

Table 1 shows the initial characteristics of the patients according to the availability of AH data (Fig. 1). Patients followed to AH and those lost to follow-up did not differ in terms of baseline characteristics, first year GH dose, or first year growth response. There was also no baseline difference between patients differing in subsequent pubertal development (Table 2). Ten percent of the patients had a bone age greater than 12 yr.

Patient characteristics at the end of treatment

Most patients followed to AH (96%) completed treatment according to France Hypophyse criteria. GH was discontinued earlier in patients with spontaneous puberty (15.4 ± 1.4 yr) than in those requiring secondary estrogen treatment or with induced puberty (16.6 ± 1.4 and 17 ± 1.4 yr, respectively). However, the total gain from the start of treatment was similar in these three groups of patients, whether expressed in centimeters or in SDS for Turner syndrome.

The mean initial GH dose was 0.7 ± 0.2 IU/kg·wk (0.23 ±

TABLE 1. Baseline and first-year characteristics of patients with Turner syndrome

Characteristic	Adult height available	
	Yes	No
No. of patients	704	187
Target height (SDS)	−0.2 ± 1.1	−0.4 ± 1.2
Birth length (SDS)	−1.9 ± 1.3	−1.9 ± 1.2
Birth weight (SDS)	−1.1 ± 1.3	−1.0 ± 1.2
Karyotype (%)		
45,X	49	48
45,X/46,XX	10	12
Other mosaicism	15	14
Other abnormalities of the X chromosome	11	8
Formulas with ring X	6	5
Formula with Y chromosome	6	7
Not available	3	6
Chronological age (yr)	11.9 ± 2.6	12.4 ± 2.4
Bone age delay (yr)	2.0 ± 1.4	2.3 ± 1.3
Height (cm)	126.0 ± 11.0	128.0 ± 10.0
Height (SDS, general population)	−3.4 ± 1.0	−3.6 ± 1.0
Height (SDS, Turner syndrome)	0.3 ± 1.0	0.2 ± 1.0
Growth velocity before treatment (cm/yr)	3.8 ± 1.6	3.6 ± 1.6
Weight (SDS, Turner syndrome)	0.5 ± 1.3	0.3 ± 1.1
Projected adult height (cm)	141.5 ± 5.0	140.9 ± 5.2
First-year GH dose (IU/kg·wk)[a]	0.7 ± 0.2	0.7 ± 0.2
First-year growth on GH (cm/yr)	6.2 ± 1.8	6.2 ± 1.8
First-year gain on GH (SDS, general population)	0.3 ± 0.4	0.3 ± 0.3
First-year gain on GH (SDS, Turner syndrome)	0.6 ± 0.3	0.6 ± 0.3

Mean ± SD are shown.
[a] To convert to mg/kg·wk, multiply by 0.33.

0.06 mg/kg·wk), with dose tending to increase during puberty (Table 2). The mean number of injections per week was 6.0 ± 0.5, with 55% of patients using up to six injections per week and 45% using more than six injections per week (*i.e.* seven injections per week during at least part of the treatment).

Puberty and pubertal growth (Table 2)

Puberty began earlier in patients with spontaneous puberty (12.5 ± 1.6 yr) than in those with secondary estrogen treatment (13.6 ± 1.7 yr) or induced puberty (15.0 ± 1.9 yr). As expected from the variable ages at pubertal onset, pubertal growth varied according to pubertal development; those with spontaneous puberty grew more than those with induced puberty (15.0 ± 5.9 *vs.* 12.5 ± 6.7 *vs.* 8.7 ± 5.9 cm). Unexpectedly, the frequency of the 45,X karyotype was lower in those with induced (46%) puberty than in those with spontaneous puberty (58%). Most patients with induced puberty were given ethinyl estradiol, with progestin introduced 2.5 ± 1.6 yr later (Table 3). Management seemed to differ for the minority of patients receiving percutaneous estrogens who started pubertal induction at a later age.

AH and predictive models

The mean AH of our cohort (n = 704) was 149.9 ± 6.1 cm, 8.5 cm above the projected height, after a mean total follow-up of 9.3 ± 2.9 yr (Fig. 2). Because height is affected by multiple, interdependent variables, we constructed a multivariate model for the analysis of AH determinants (Table 4). In the final model, 90% of AH variance was accounted for by factors classified into four categories. Age at treatment initiation and treatment duration were independently associated with outcome, with coefficients of 3.1 and 1.5 cm/yr, respectively. These two factors accounted for 66% of the outcome variance in the final model, but were not independent, making it difficult to decipher how each of them influences outcome. When each was alternatively left out of the model, the influence of the other increased. In all cases, the influence of age was roughly twice as high as the influence of treatment duration (in Table 4: age, 3.1 cm/yr; duration, 1.5 cm/yr; in models with only one variable: age, 4 cm/yr; duration, 2.5 cm/yr). Age at onset of puberty had a significant, but modest, effect, with a delay of 1 yr being associated with an AH gain of 0.3 cm. GH dose and number of injections per week were independent predictors. Most (90%) of the patients received a mean dose of 0.5–0.9 U/kg·wk (0.17–0.30 mg/kg·wk). The logarithmic relationship between dose and height gain implies that a 0.2 U/kg·wk (0.06 mg/kg·wk) change in dose was associated with a gain in height of 0.8 cm for the range 0.5–0.7 U/kg·wk (0.17–0.23 mg/kg·wk) and with a gain of 0.6 cm for the range 0.7–0.9 U/kg·wk (0.23–0.30 mg/kg·wk). Similarly, patients receiving more than six injections per week grew 0.8 cm more than those receiving up to six injections per week. Several other variables were tested and found not to be predictors of AH in this model. These variables included birth weight, age squared, karyotype, presence of dysmorphic features or Turner syndrome-associated morbidity, and type of pubertal development. If age at onset of puberty was left out of the model, type of pubertal development was still not associated with outcome.

Because age at onset of puberty appeared to be predictive, but was, in fact, a composite of age at spontaneous puberty and age at estrogen administration, we repeated the analysis using only patients with induced puberty to concentrate on the influence of medically induced pubertal development. Our first analysis gave results similar to those of the general model, except that age at onset of puberty was just below the significance threshold (0.2 cm/yr; 95% confidence interval, −0.02 to 0.51; $P = 0.076$). Percutaneous estradiol was the only type of estrogen treatment independently associated with outcome, resulting in AHs 2.1 cm higher than with other types of treatments ($P = 0.0003$; 95% confidence interval, 1.0–3.2). Time to introduction of progestin treatment was not associated with outcome.

Discussion

We analyzed a population-based cohort of patients with Turner syndrome treated with GH to AH. Our main findings were 1) treatment increases AH by a mean of 8.5 cm over projected height, based on specific normative data; 2) age and treatment duration accounted for most of the outcome variance; 3) GH dose, number of weekly injections, age at onset of puberty, and type of estrogen used had independent effects on AH; and 4) age at medically induced puberty had no influence on AH.

In this study we were able to follow 79% of a well-defined population of patients to AH, taking a large number of clin-

TABLE 2. Height outcome of patients with Turner syndrome according to pubertal development

Characteristic	Spontaneous puberty		Induced puberty
	No secondary estrogen treatment	Secondary estrogen treatment	
At GH initiation			
No. of patients	69	84	522
Target height (SDS)	−0.7 ± 1.1	−0.2 ± 1.2	−0.2 ± 1.1
Birth length (SDS)	−1.9 ± 1.2	−2.0 ± 1.2	−1.9 ± 1.3
Karyotype (%)			
45,X	55	56	49
45,X/46,XX	13	6	10
Other mosaicism	17	19	15
Other abnormalities of the X chromosome	6	6	11
Formulas with ring X	6	6	6
Formula with Y chromosome	0	2[a]	6
Not available	3	5	3
Chronological age (yr)	11.0 ± 2.2	11.7 ± 2.4	11.9 ± 2.6
Bone age delay (yr)	1.6 ± 1.2	1.7 ± 1.2	2.0 ± 1.4
Height (cm)	123.8 ± 10.5	124.8 ± 10.9	126.4 ± 11.1
Height (SDS, general population)	−3.1 ± 1.0	−3.5 ± 1.0	−3.4 ± 1.0
Height (SDS, Turner syndrome)	0.4 ± 1.1	0.1 ± 1.1	0.3 ± 1.0
Growth velocity (cm/yr)	4.2 ± 1.8	4.0 ± 1.7	3.7 ± 1.5
Projected adult height (cm)	141.7 ± 5.9	140.7 ± 5.8	141.5 ± 5.3
At end of GH treatment			
Age (yr)	15.4 ± 1.4	16.6 ± 1.4	17.0 ± 1.4
Height (cm)	146.1 ± 7.4	147.1 ± 6.3	148.7 ± 6.0
Duration of GH therapy (yr)	4.5 ± 1.9	4.9 ± 2.3	5.0 ± 2.2
Mean GH dose (IU/kg·wk)[b]	0.7 ± 0.1	0.8 ± 0.1	0.8 ± 0.2
No. of GH injections per week (n)[c]	6.1 ± 0.5	6.1 ± 0.4	6.0 ± 0.5
6 or less (%)	44	54	56
6 to 7 (%)	52	39	39
7 (%)	4	7	5
Height (SDS, general population)	−2.6 ± 1.2	−2.7 ± 1.0	−2.5 ± 1.0
Height (SDS, Turner syndrome)	1.9 ± 1.3	1.8 ± 1.1	2.0 ± 1.1
Height gain (cm)	22.8 ± 10.5	22.4 ± 11.1	22.2 ± 10.9
Height gain (SDS, general population)	0.5 ± 0.7	0.8 ± 0.9	0.9 ± 0.8
Height gain (SDS, Turner syndrome)	1.6 ± 0.8	1.6 ± 0.8	1.7 ± 0.8
Pubertal growth			
Age at onset of puberty (yr)	12.5 ± 1.6	13.6 ± 1.7	15.0 ± 1.9
Bone age delay at onset of puberty (yr)	1.5 ± 1.3	1.9 ± 1.4	2.7 ± 1.5
Height at pubertal onset (cm)	133.1 ± 7.8	136.1 ± 8.1	141.8 ± 7.9
Height at pubertal onset (SDS, general population)	−2.8 ± 1.2	−3.1 ± 1.1	−3.0 ± 1.0
Height at pubertal onset (SDS, Turner syndrome)	1.1 ± 1.3	1.0 ± 1.2	1.4 ± 1.1
Total pubertal growth (cm)	15.0 ± 5.9	12.5 ± 6.7	8.7 ± 5.9
Pubertal growth on growth hormone (cm)	13.0 ± 6.3	11.0 ± 6.1	6.8 ± 5.8
Total pubertal growth (SDS, general population)	0.1 ± 1.0	0.5 ± 1.0	0.7 ± 0.7
Total pubertal growth (SDS, Turner syndrome)	0.5 ± 0.9	0.7 ± 1.0	0.6 ± 0.7
Prepubertal growth hormone treatment duration (yr)	1.6 ± 1.8	2.1 ± 2.1	3.0 ± 2.1
Postpubertal growth hormone treatment duration (yr)	2.9 ± 1.2	2.9 ± 1.3	2.0 ± 1.5
GH dose before puberty (IU/kg·wk)[b]	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.2
GH dose during puberty (IU/kg·wk)[b]	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2
At AH			
Age (yr)	20.3 ± 2.7	20.3 ± 2.4	21.4 ± 2.9
Adult height (cm)	148.0 ± 7.3	148.5 ± 6.2	150.5 ± 5.9
Adult height (SDS, general population)	−2.7 ± 1.3	−2.6 ± 1.1	−2.3 ± 1.0
Adult height (SDS, Turner syndrome)	1.6 ± 1.4	1.7 ± 1.2	2.0 ± 1.1
Height gain (cm)	24.8 ± 10.2	23.7 ± 11.0	24.1 ± 10.7
Height gain (SDS, general population)	0.4 ± 1.0	0.9 ± 1.0	1.1 ± 0.9
Height gain (SDS, Turner syndrome)	1.2 ± 1.0	1.5 ± 1.0	1.8 ± 0.9
Height gain over projected height (cm)	6.3 ± 5.2	7.9 ± 5.1	9.0 ± 4.4

[a] Gonadectomy was performed in these two patients right after the onset of pubertal development.
[b] To convert to mg/kg·wk, multiply by 0.33.
[c] The number of injections per week could vary with time.

ical, auxological, and therapeutic parameters into account in the analysis, rendering this study the most comprehensive to date. Our patients were followed in daily practice, so our results are not subject to the inclusion biases inherent to clinical trials. Two limitations of our study are the later mean age at treatment initiation than in other studies and the observational nature of data collection. However, this late age at initiation of treatment reflects the nature of the study,

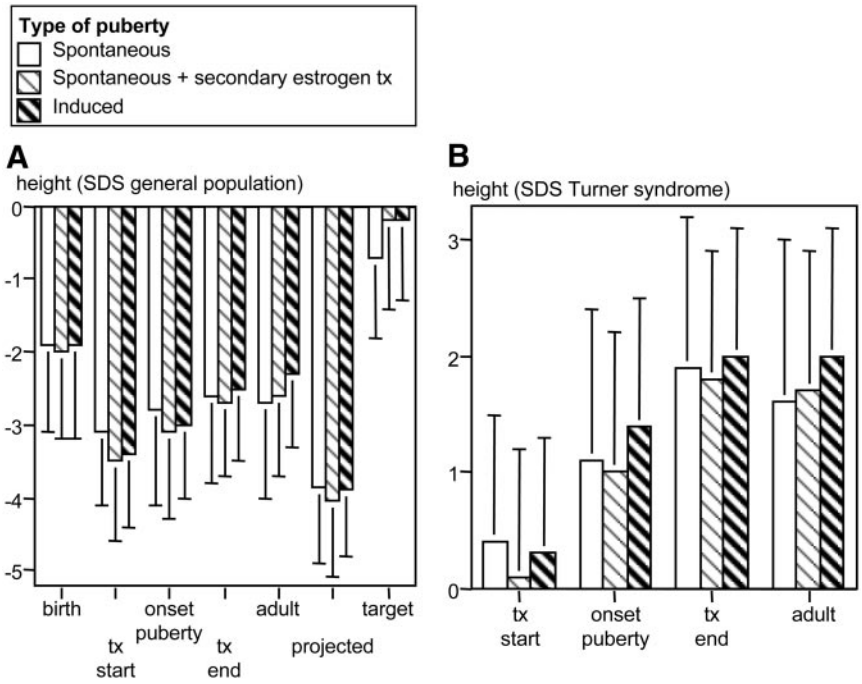

FIG. 2. Evolution of height in GH-treated patients with Turner syndrome. The mean ± SD are presented, and data are divided according to the type of pubertal development: A, height expressed as SDS for the general population; B, height expressed as SDS for Turner syndrome. □, Spontaneous puberty; ▨, spontaneous onset of puberty and secondary estrogen treatment; ▩, induced puberty. tx, Treatment.

an analysis of a population-based cohort including all treated patients, even those treated late and for only a few months (as opposed to clinical trials with fixed inclusion criteria), and the selection of subjects who have attained AH. Indeed, 10% of patients had a bone age superior to 12 yr at the onset of treatment, in violation of the eligibility criteria, but were maintained in the analysis. Age at initiation of treatment and duration of treatment were predictors of AH, also demonstrating the value of early treatment to increase AH. However, 95% of children had an age at initiation of treatment between 7 and 16 yr. Whether starting earlier than age 7 yr would result in a greater gain in AH remains to be demonstrated.

Our results extend to a population-based cohort findings obtained in clinical trials (11, 13, 14, 17, 18), clinic-based series (15, 19), and international postmarketing databases (12, 16), adding several new observations with important implications for daily practice. Most published studies indicate a gain over predicted height, but variable settings preclude direct comparison. Similarly, comparing the factors associated with height in these reports is difficult, given the differences in methodology. In our study age at treatment initiation and treatment duration were both identified as predictors, but younger age seemed to be more strongly associated with outcome than duration of treatment. However, we must acknowledge that separating the two effects is nearly impossible in the context of such an observational study. Previous studies (12, 14–18, 20) have similarly detected the influence of age at treatment initiation, whereas another study has not detected it (19). Bone age delay and weight at baseline were identified as independent predictors in a previous study (17). This suggests that adipose tissue

TABLE 3. Pubertal growth in patients with induced puberty according to the type of estrogen used

	Oral ethinyl estradiol	Oral estradiol	Percutaneous estradiol	Estrogen-progestin combinations
No. of patients[a]	315	144	45	7
Age at estrogen treatment (yr)	14.6 ± 1.9	15.4 ± 1.8	16.0 ± 1.5	16.8 ± 1.7
Delay between estrogens and progestin (yr)				
<1	13%	29%	35%	
1–2	36%	50%	49%	
>2	51%	21%	16%	
Duration of GH before estrogens (yr)	2.5 ± 1.9	4.0 ± 2.1	3.6 ± 1.9	3.6 ± 2.1
Duration of GH after estrogens (yr)	2.3 ± 1.5	1.6 ± 1.0	1.3 ± 1.1	0.4 ± 1.6
Height at initiation of estrogen treatment (SDS, general population)	−3.1 ± 1.0	−2.7 ± 1.0	−2.8 ± 1.1	−2.7 ± 1.3
Height at initiation of estrogen treatment (SDS, Turner syndrome)	1.2 ± 1.1	1.9 ± 1.1	1.7 ± 1.1	1.8 ± 1.4
Pubertal growth (cm)	10.1 ± 6.5	6.8 ± 3.6	6.4 ± 4.3	5.0 ± 4.2
Pubertal growth on GH (cm)	8.0 ± 6.4	5.3 ± 3.8	4.6 ± 4.0	2.5 ± 4.8
AH (cm)	150.0 ± 5.8	151.4 ± 6.0	152.4 ± 5.2	151.8 ± 6.0
Gain over projected height (cm)	8.4 ± 4.5	9.6 ± 4.0	11.2 ± 3.6	8.4 ± 3.6

[a] Data for estrogen therapy are not available for 193 patients.

TABLE 4. Factors associated with AH in Turner syndrome patients treated with GH

Variable	Regression coefficient[a]	95% Confidence interval	*P*	% Variance explained
Regression toward the mean				
Height at baseline (a, cm)	0.13	0.01/0.25	0.033	1.1
Total duration of follow-up (b, yr)	1.54	0.24/2.84	0.020	1.3
Interaction (a × b)	−0.01	−0.02/0.00	0.051	0.9
Constitutive				
Birth length (SDS)	0.28	0.07/0.50	0.011	1.5
Target height (SDS)	0.56	0.28/0.84	<0.0001	3.6
Baseline				
Age at baseline (yr)	−3.06	−3.49/−2.63	<0.0001	44.6
Weight at baseline (SDS)	−0.47	−0.76/−0.17	0.002	2.3
Bone age delay (yr)	0.87	0.57/1.17	<0.0001	7.4
Puberty and treatment related				
Age at onset of puberty (yr)	0.28	0.08/0.49	0.006	1.7
Duration of GH (yr)	1.54	1.22/1.85	<0.0001	21.3
Log GH dose (IU/kg·wk)	2.42	0.99/3.86	0.001	2.5
No. of injections per week >6 (yes = 1, no = 0)	0.81	1.36/0.26	0.004	1.9

Number of patients in the final model corresponding to those with no missing value for any predictor variable n = 547; $r^2 = 0.9$.
[a] The regression coefficient represents the change in centimeters per unit change in predictor.

plays a role in regulating skeletal growth, as observed in the general population (16). Childhood adiposity is thought to affect the pubertal growth spurt by interacting with the gonadal axis; the similar relationship observed in agonadal patients with Turner syndrome suggests either that steroids of adrenal origin may be aromatized by fat cells or that another pathway links fat and bone (32, 33).

GH dose is also a matter of debate in the management of Turner syndrome, and clinical trials have shown that the AH gain is dose dependent (13, 17, 18). We confirmed that dose had an effect, but the logarithmic relationship between dose and height implies that the effect of the same absolute increase is weaker at higher doses than at lower doses. Unexpectedly, we found that the use of more than six, as opposed to six, injections per week was associated, independently of mean weekly dose, with a height gain of 0.8 cm, which is larger than that obtained by increasing the dose from 0.7 to 0.9 IU/kg·wk. This finding extends previous results comparing three injections with six or seven injections per week (34) and suggests that daily injections are the treatment strategy of choice for optimal growth.

Finally, our data made it possible to investigate the effect of pubertal development on growth in a large series of patients. One limitation of our analysis is that our definition of pubertal onset was not the same in the various pubertal groups (age at breast development in those with spontaneous puberty and age at initiation of estrogen treatment in those with induced puberty). However, additional exploratory analyses indicated that this had not biased our conclusions. Given the earlier mean age at onset of puberty in those with spontaneous pubertal development, only multivariate analysis could determine whether age and type of pubertal development had independent effects; we found that age had a moderate effect (0.3 cm/yr), but that type of pubertal development had no independent effect even when age at pubertal onset was left out of the model. This contrasts with several other studies that did not take into account both factors (15, 16, 19). Type of pubertal development was not associated with height if age at onset of puberty was left out of the model, but might indirectly affect outcome by interacting with the duration of treatment. However, age at medically induced puberty was not associated with AH in our analysis of patients with induced puberty, although the range of age at treatment initiation was wide, with 93% of patients first receiving estrogens between the ages of 12 and 18 yr. Other cohort studies also found no effect of age at estrogen treatment initiation (16, 19), whereas Chernausek *et al.* (14) observed a 3.3-cm difference, whether estrogen treatment was initiated at the age of 15 or 12 yr, as part of a clinical trial. The use of different estrogen preparations might account for these differences. Our results together with the well-established effects of estrogens on behavior (23), motor function, cognition (35), and bone mineralization (24) suggest that estrogens should be introduced at a physiologically appropriate age in patients with Turner syndrome. The late initiation of estrogen treatment was associated with lower health-related quality of life in our recent study (36).

We also evaluated the effect on growth of the type of estrogen used. In accordance with a recent survey of prescribing practices in Europe (37), we found that various estrogen treatments were prescribed, with a minority of patients using transdermal estradiol. Unexpectedly, transdermal estrogen use was associated with a 2.1-cm greater AH. However, this association could not be causal, given a number of potential confounders. Previous reports have shown good tolerance and physiological plasma estradiol levels in patients using gel (38) or patches (39). The negative effects of oral (*vs.* transdermal) estrogens on plasma IGF-I levels are consistent with our observations (40). The influence of route of estrogen administration on height should be tested through prospective trials, but meanwhile, our results suggest that the use of percutaneous estrogens is associated with a better outcome.

In conclusion, our auxological analysis indicates that height gain depends on the age at GH treatment initiation and treatment duration and supports the practice of pharmacologically inducing puberty at a physiological age. However, our results should be seen in the context of the absence

of a demonstrated effect of height on health-related quality of life and the deleterious effects of overexpectations from treatment (36, 41). These considerations together with treatment cost should be put into perspective with current uncertainties regarding long-term safety and the need for long-term surveillance of treated patients.

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