Height Gain in Ullrich-Turner Syndrome after Early and Late Growth Hormone Treatment Start: Results from a Large Retrospective German Study and Potential Basis for an Individualized Treatment Approach

Markus Bettendorf^a Ioana M. Inta^a Helmuth G. Doerr^b Berthold P. Hauffa^c
Otto Mehls^a Michael B. Ranke^d

^aHospital for Children and Adolescents, University of Heidelberg, Heidelberg, ^bHospital for Children and Adolescents, University of Erlangen, Erlangen, ^cDepartment of Pediatric Endocrinology and Diabetology, University Children's Hospital, University of Duisburg-Essen, Essen, and ^dChildren's Hospital, University of Tuebingen, Tuebingen, Germany

Key Words

Growth hormone treatment · Late treatment start ·
Ullrich-Turner syndrome · Adult height · Height prediction

Abstract

Background: Ullrich-Turner syndrome (UTS) girls often present with short stature in adolescence to the endocrinologist when the efficacy of growth hormone (GH) to improve growth remains unknown and parameters to estimate individual GH responsiveness have yet to be determined. **Objective:** Retrospective evaluation of adult height (AH) and predicted adult height at GH start (descriptive model of Ranke, Model PredAH) in early and late GH-treated German UTS patients. **Subjects/Methods:** 313 patients treated with GH, early [chronological age (CA) at GH start <12 years, n = 259] or late (CA at GH start ≥12 years, n = 54) who reached AH were selected from KIGS (Pfizer International Growth Database). **Results:** AH (152.5 ± 5.9 vs. 151.1 ± 5.4 cm, $p = \text{n.s.}$) after GH treatment for 7.5 ± 2.12 years (GH start early) and for 5.2 ± 1.2 years (GH start late) were similar ($p = \text{n.s.}$) as Model PredAH (155.7 ± 4.8 vs. 154.7 ± 4.8 cm;

$p = \text{n.s.}$) but higher ($p < 0.001$) than projected adult height (Ranke, ProjAH; 148.2 ± 5.5 vs. 145.2 ± 6.7 cm; $p = 0.001$). Total height gain over ProjAH was 4.3 ± 4.6 cm (GH start early) and 5.8 ± 4.7 cm (GH start late, $p = 0.021$), respectively. **Conclusions:** GH may improve AH in UTS patients even when started late. The individual growth response could be estimated by the descriptive Model PredAH independent of age at treatment start.

© 2013 S. Karger AG, Basel

Introduction

Growth hormone (GH) treatment improves growth and final height in short girls with Ullrich-Turner syndrome (UTS) [1–4]. However, the response to GH is rather variable which may be explained by different treatment protocols such as dosing regimens, adjuvant therapy with oxandrolone, age at start of GH therapy and management of puberty. GH dose and age at initiation of GH treatment are among the most important factors for a beneficial outcome [5]. Management of puberty was also studied in de-

tail. After starting estrogen treatment for the induction of puberty further height gain may be limited [5–7], but other studies investigating the age at induction of puberty suggested different results [8, 9]. The actual therapeutic guidelines [10] recommend an early initiation of GH treatment after the age of 2 years as soon as the height of a patient with UTS falls below the third percentile of the growth chart for healthy females. The treatment with estrogens for the induction of puberty is recommended to be started at 12 years, but not later than 15 years, in order to avoid a delay in pubertal development [11, 12].

There are still some girls with UTS who are diagnosed late and are presented to the pediatric endocrinologist in adolescence, when the effectiveness and individual responsiveness of GH treatment are a matter of debate [13, 14]. Up to now there are no strategies to manage growth and puberty in older patients with UTS. Therefore, we analyzed retrospectively adult height (AH) and predicted adult height (Model PredAH) in German UTS patients documented in the KIGS database after early and late GH treatment start.

Patients and Methods

German girls with UTS who were documented in the pharmacoepidemiological survey KIGS were extracted from the database for further analyses. KIGS is an international registry developed with the primary objective to record long-term efficacy and safety of recombinant human GH, Genotropin® (Pfizer Inc., New York, N.Y., USA). KIGS is conducted in accordance with the Declaration of Helsinki [15].

313 UTS patients from 96 German centers who reached AH (bone ages >14 years according to Greulich and Pyle (GP) [16] and/or height velocities <2 cm/year at their latest visits) were identified. The patients were grouped according to their chronological ages at GH treatment start: before (n = 259) and equal or after (n = 54) 12 years of age. This cut-off was deduced from prior analyses of the mean chronological age at the start of puberty for the normal female population (11.2 ± 1.1 years) [17]. The diagnoses of UTS were confirmed by karyotype analyses as listed in table 1.

Anthropometric data were extracted from the KIGS database: birth lengths (cm), birth weights (g), parental heights (cm) and heights (cm), weights (kg) and bone ages at start of GH therapy, at start of puberty and at last visits (AH). Percentiles and standard deviation scores (SDS) were extrapolated based on specific references by Niklasson et al. [18] for birth weights and birth lengths, by Freeman et al. [19] for weight and BMI, by Ranke et al. [20] for UTS-specific heights and by Reinken and van Oost [22] for normal heights. AH SDS were calculated based on adult UTS references [20] and on normal adult references [21]. Puberty onset was defined as the first time of reported breast stage $\geq$ B2 or the time when estrogen replacement started.

At GH start, projected adult heights (Ranke, ProjAH) [20], prospective final heights (Bayley-Pinnaeu, BP) [22] and predicted

Table 1. Karyotypes and their relative frequencies in the patients (n = 313) grouped by the age at treatment start (early, n = 259 and late, n = 54; p = n.s.)

Karyotype	Early GH start (n = 259) (%)	Late GH start (n = 54) (%)
45,X	52.9	55.6
46,XXq-	0.4	0
46,X,I (Xq)	8.5	9.3
45,X/46,XX	6.6	3.7
45,X/46,X,r(X)	1.5	1.9
45,X/46,X,i(X)	11.6	9.3
Other mosaics	8.1	13
45,X/46,XY	0	1.9
Others	5.0	1.9

heights (descriptive KIGS model of Ranke, Model PredAH) [23] were calculated and compared to AH (cm and syndrome-specific SDS). ProjAH was calculated assuming that in untreated patients with UTS the spontaneous disease-specific AH SDS corresponds to the disease-specific height SDS at presentation [20], prospective final height (BP) was calculated based on the bone age rating (GP) at GH start [22] and Model PredAH was calculated utilizing the descriptive model for Turner patients treated with GH [23].

Model PredAH – based on the descriptive model of Ranke et al. [23] – includes the prediction of the first year on GH and was calculated as follows: $AH\ (cm) = 142.9 + (MPH\ SDS \times 1.37) + [height\ SDS\ at\ GH\ start\ (TS) \times 4.11] + [studentized\ residual\ during\ 1st\ year\ of\ treatment \times 1.99] + [mean\ GH\ dose\ (mg/kg/week) \times 4.82] + [age\ at\ start\ of\ puberty\ (years) \times 0.74]$. This equation explains 67% of variability of AH with an error SD of 3.6 cm [23, 24]. Pubertal growth was analyzed in terms of observed and predicted total pubertal growth (TPG) as described previously [25]. Total height gains were calculated as the differences between AH and ProjAH.

Statistical Analysis

Data are expressed as mean $\pm$ SD. Statistical analysis was performed by Wilcoxon and Fisher tests and χ^2 test. The results were considered significant at $p < 0.05$. SAS® version 8 for Sun Solarix (SAS Institute, Cary, N.C., USA) was used for all statistical analyses.

Results

The relative frequency of documented karyotypes was not different between patients with early and late start of GH treatment (table 1). Modalities of GH treatment are depicted in table 2. While GH doses and frequencies were comparable in the two treatment groups, duration of treatment was significantly shorter in the late-start GH treatment group.

Table 2. Modalities of GH therapy in the patients (n = 313) grouped by the age at treatment start (early, n = 259 and late, n = 54); variables are presented as mean $\pm$ SD

Variable	Early GH start (n = 259)	Late GH start (n = 54)	p
Mean total dose, mg/kg/week	0.3 $\pm$ 0.1	0.3 $\pm$ 0.1	0.003
Frequency of injections/week	7.0 $\pm$ 0.1	7.0 $\pm$ 0.1	0.017
Therapy time, years	7.5 $\pm$ 2.12	5.2 $\pm$ 1.2	<0.001
Oxandrolone, %	0.8 (at GH start)	0 (at GH start)	
	15.1 (at last visit)	14.8 (at last visit)	n.s.
Thyroxine, %	0.8 (at GH start)	1.9 (at GH start)	
	18.1 (anytime during treatment)	14.8 (anytime during treatment)	n.s.
Chronological age at start of puberty, years	13.3 $\pm$ 1.4	15.4 $\pm$ 1.8	<0.001

The auxological characteristics of all patients at birth, at the time of GH start, after 1 year of GH treatment, at start of puberty and at AH are outlined in table 3.

While birth weights and birth lengths were similar in early and late GH-treated patients, parental heights were significantly higher in early treated patients (table 3).

At GH start, chronological ages and bone ages were significantly different in the two groups as were heights. Bone ages were more retarded compared to chronological ages in late GH-treated patients. BMI were comparable at GH start in early and late treated patients. ProjAH and BP were similar in the patients groups but higher in early treated patients. Model PredAH were comparable in the two groups but higher than ProjAH and BP (table 3).

Heights of all patients improved after 1 year of GH treatment and thereafter until start of puberty and further to AH (table 3; fig. 1).

At start of puberty, patients of the late treatment start group were significantly older than early treated patients whereas bone ages and heights (cm) were similar (table 3; fig. 1). Puberty was induced with estrogens in 72.2% (early GH start) and 83.3% (late GH start) of the patients, respectively. Again, no differences in BMI were observed between the two groups at start of puberty (table 3).

AH were comparable in both treatment groups and similar to Model PredAH which were greater than ProjAH (fig. 2). The total height gain over ProjAH was 4.3 $\pm$ 4.6 cm in early GH-treated patients and 5.8 $\pm$ 4.7 cm in late GH-treated patients (p $\leq$ 0.021) (table 3). At AH, late treated patients were significantly older than early treated patients, but no difference between their bone ages was noticed.

Height velocities (cm/year) during the first treatment year were significantly higher in early treated patients compared to late treated patients whereas TPG (cm) were

similar in the two groups (table 3). However, observed TPG was higher than expected in the late treated group. BMI SDS slightly increased during GH treatment to a similar extent in both groups (table 3).

Discussion

In this retrospective study, German UTS patients documented in the KIGS database who had reached AH after GH treatment were analyzed dependent on the age at start of GH treatment in order to evaluate the efficacy of late GH treatment start in adolescence and to assess the significance of a prediction model in selecting GH-responsive patients at early and late treatment start.

GH treatment in UTS girls aims at early catch-up growth in childhood, at near normalization of height before puberty and finally at an increase of AH. Current guidelines for GH treatment of short stature in UTS recommend a treatment start at an early age as soon as the height falls below the third percentile of the specific reference growth chart and to initiate treatment with estrogens between the chronological ages of 12–13 years [10, 12]. However, more than 20% of UTS patients are diagnosed beyond the age of 11 years, most of them with a serious height deficit and delayed or arrested puberty [13, 14]. These patients have then missed the opportunity of early GH treatment and failed the option of normalization of height during childhood and of age-appropriate induction of puberty. The age at initiation of GH treatment as well as the age and the height at puberty onset and duration of GH treatment are important prognostic factors for final height in UTS [5, 9, 10, 26–28]. Our present study as well as a previous report on late GH therapy in UTS girls analyzing first-year height velocities (n =

Table 3. Background characteristics and anthropometric variables of the patients (n = 313) at GH start, after first year of therapy, at start of puberty and at AH grouped by the age at treatment start (early, n = 259 and late, n = 54)

Variable	Early GH start		Late GH start		p
	n	mean ± SD	n	mean ± SD	
Background					
Birth weight, SDS	240	−1.2±1.2	51	−0.9±1.4	n.s.
Birth length, SDS	241	−0.6±1.3	48	−0.5±1.7	n.s.
Gestational age, weeks	242	39.2±1.7	52	39.0±1.6	n.s.
Target height (TH), cm	259	164.2±5.5	54	162.6±5.1	0.04
TH, SDS, normal reference	259	−0.6±1.1	54	−0.9±1.0	0.04
At GH start					
Chronological age, years	259	8.5±2.2	54	13.2±1.1	<0.001
Bone age GP, years	233	7.4±2.5	53	10.8±1.4	<0.001
Height, cm	259	114.8±11.9	54	130.8±6.2	<0.001
Height, SDS, normal reference	259	−3.4±0.8	54	−4.4±1.2	<0.001
Height, SDS*	259	0.3±0.9	54	−0.2±1.1	0.001
BMI, SDS	259	0.4±1.1	54	0.4±1.1	n.s.
ProjAH, cm	259	148.2±5.5	54	145.2±6.7	0.001
ProjAH, SDS*	259	0.3±0.9	54	−0.2±1.1	0.001
BP, cm	162	147.6±5.5	51	145.9±5.4	0.045
BP, SDS*	162	0.2±0.9	51	−0.1±0.9	0.045
Model PredAH, cm	259	155.8±4.8	54	154.7±4.8	n.s.
Model PredAH, SDS*	259	1.6±0.8	54	1.4±0.8	n.s.
After 1 year GH					
Height, cm	259	122.8±11.6	54	137.2±6.0	<0.001
Height, SDS*	259	1.1±0.9	54	0.4±1.1	<0.001
Height velocity, cm/year	259	8.0±1.5	54	6.4±1.2	<0.001
Δ Height, SDS, normal reference	259	0.6±0.3	54	0.1±0.3	<0.001
Δ Height, SDS*	259	0.8±0.3	54	0.6±0.2	<0.001
Studentized residuals (SR)	243	−0.2±1.1	37	−0.2±1.0	n.s.
At start of puberty					
Chronological age, years	227	13.3±1.4	48	15.4±1.8	<0.001
Bone age GP, years	213	12.1±1.2	46	12.3±1.1	n.s.
Height, cm	227	143.3±7.7	48	142.2±6.7	n.s.
Height, SDS*	227	2.1±1.1	48	0.7±1.0	<0.001
BMI, SDS	226	0.6±1.1	48	0.4±1.3	n.s.
Adult height					
Chronological age, years	259	16.6±1.3	54	18.8±1.6	<0.001
Bone age GP, years	147	15.0±1.0	29	15.3±1.1	n.s.
Height, cm	259	152.5±5.9	54	151.1±5.4	n.s.
Height, SDS, adult reference*	259	1.0±1.0	54	0.8±0.9	n.s.
Height, SDS, normal reference	259	−2.8±1.2	54	−3.1±1.1	n.s.
BMI, SDS	258	0.8±1.1	53	0.8±1.2	n.s.
TPG, cm, observed	149	10.5±5.7	30	9.7±5.3	n.s.
TPG, cm, predicted	149	10.5±4.1	30	6.5±4.8	<0.001
SR puberty	149	0.0±1.1	30	1.1±1.2	<0.001
Total height gain, cm, AH-ProjAH*	259	4.3±4.6	54	5.8±4.7	0.021

Variables are presented as mean $\pm$ SD. * Height SDS UTS [20], normal reference [21].

Fig. 1. Heights (cm) at GH treatment start, after 1 year of treatment, at puberty start and adult height (AH) for early treated patients (E, $n = 259$) and late treated patients (L, $n = 54$). Box plots represent 10th, 25th, 50th, 75th, 90th percentiles. Dots indicate respective means.

Fig. 2. At GH start actual heights (cm), ProjAH, Model PredAH and adult height (AH) for early treated patients (E, $n = 259$) and late treated patients (L, $n = 54$). Box plots represent 10th, 25th, 50th, 75th, 90th percentiles. Dots indicate respective means.

345) and near AHs ($n = 28$) from KIGS clearly indicate that late initiation of GH therapy shows robust height improvement [29] disproving a preceding single center study which reported no further height gains after puberty onset in 42 UTS patients [5]. The appropriate age to induce puberty in UTS patients remains a matter of debate [8, 30, 31]. Initiation of GH treatment early allows timely estrogen supplementation and prevents further height loss in childhood and adolescence and therefore might reduce the psychological harm of short stature and hypogonadism [33, 34]. This goal can be reached when UTS patients are diagnosed and treated with GH early, e.g. before 12 years of age [34]. Some reports suggested that even low estrogens levels lead to skeletal maturation and compromise final height, but delayed administration of estrogens prolongs growth before puberty [36–38]. In our present study, estrogen therapy was started in the late GH treatment group at a mean age of 15.4 years compared to 13.3 years in the early treatment group and observed TPG was similar as in early treated patients which

may explain why late treated patients had more total height gain than early treated patients resulting in similar AH (152.5 vs. 151.1 cm). This is in accordance with previous reports, which revealed a beneficial effect of GH treatment even during late estrogen supplementation in UTS patients [39, 40]. In contrast, low-dose estrogens alone failed to improve final heights in UTS patients [41, 42]. Therefore, late GH treatment start seems to be justified in UTS patients and appropriate tools such as prediction models should be identified to estimate individual responsiveness before start of GH treatment in order to quantify treatment expectations of patients, physicians and healthcare providers.

Several models were reported to predict the effect of GH treatment [23, 32]. The prediction of growth responses in these models is based mainly on auxological and endocrine parameters [23, 32]. GH dose was the most important predictor for height velocity in the first year of GH treatment in UTS patients. Thereafter, the height velocity in the previous year is the most important predictor

of the final outcome [23, 24]. Based on this model it was suggested that the individual first-year response determines the AH most. In our study, first-year height velocities of early treated patients were higher than first-year height velocities of late treated patients. We evaluated retrospectively Model PredAH as a tool to select GH-responsive patients at GH treatment start. AH varied considerably but were similar in all patients treated with GH, independent of age at treatment start, and significantly above the average AH for German UTS references and ProjAH [20]. The variability of AH indicate that UTS patients in fact respond differently to GH treatment. In both groups the descriptive model predicted a very similar AH at start of treatment despite the fact that patients who were treated late were significantly older at start of treatment, at start of puberty and at AH in comparison to the group used for model development. Apart from that, bone ages and heights (cm) at start of puberty were similar in both groups. These results and others indicate that Model PredAH can represent a reliable tool to identify GH-responsive UTS patients irrespective of their age at start of GH therapy [23, 24].

In summary, this retrospective study provides strong evidence that late start of GH treatment in adolescence may still improve final heights in short girls with UTS above ProjAH. However, this regimen implies perpetuation of short stature in childhood and significant delay of pubertal development. Therefore, GH treatment start should not be delayed until adolescence. However, our results indicate that adolescent UTS patients with short stature should not be excluded a priori from GH treatment. Model PredAH can estimate GH-stimulated growth in UTS patients before and in the course of adolescence and may therefore represent a tool to estimate individual responsiveness before start of GH treatment in order to quantify treatment expectations of patients, physicians and healthcare providers even when their diagnosis was missed in childhood.

Acknowledgment

The authors would express their thanks to the German KIGS clinicians who provided the data on their patients.

References

- 1 Cave CB, Bryant J, Milne R: Recombinant growth hormone in children and adolescents with Turner syndrome. *Cochrane Database Syst Rev* 2003;3:CD003887.
- 2 Rosenfeld RG, Attie KM, Frane J, Brasel JA, Burstein S, Cara JF, Chernauek S, Gotlin RW, Kuntze J, Lippe BM, Mahoney CP, Moore WV, Saenger P, Johanson AJ: Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. *J Pediatr* 1998; 132:319–324.
- 3 Van Pieren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, Otten BJ, Hoorweg-Nijman JJ, Vulsma T, Stokvis-Brantsma WH, Rouwe CW, Reeser HM, Gerver WJ, Gosen JJ, Rongen-Westerlaken C, Drop SL: Final height in girls with Turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab* 2003;88: 1119–1125.
- 4 Stephure DK, Canadian Growth Hormone Advisory Committee: Impact of growth hormone supplementation on adult height in Turner syndrome: results of the Canadian randomized controlled trial. *J Clin Endocrinol Metab* 2005;90:3360–3366.
- 5 Schweizer R, Ranke MB, Binder G, Herdach F, Zapadlo M, Grauer ML, Schwarze CP, Wollmann HA: Experience with growth hormone therapy in Turner syndrome in a single centre: low total height gain, no further gains after puberty onset and unchanged body proportions. *Horm Res* 2000;53:228–238.
- 6 Ranke MB, Partsch CJ, Lindberg A, Dorr HG, Bettendorf M, Haufla BP, Schwarz HP, Mehls O, Sander S, Stahnke N, Steinkamp H, Said E, Sippell W: Adult height after GH therapy in 188 Ullrich-Turner syndrome patients: results of the German IGLU Follow-up Study 2001. *Eur J Endocrinol* 2002;147:625–633.
- 7 Chernauek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J: Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. Genentech, Inc., Collaborative Study Group. *J Clin Endocrinol Metab* 2000;85:2439–2445.
- 8 Johnston DI, Betts P, Dunger D, Barnes N, Swift PG, Buckler JM, Butler GE: A multicentre trial of recombinant growth hormone and low dose oestrogen in Turner syndrome: near final height analysis. *Arch Dis Child* 2001;84: 76–81.
- 9 Bechtold S, Dalla Pozza R, Schmidt H, Bonfig W, Schwarz HP: Pubertal height gain in Ullrich-Turner syndrome. *J Pediatr Endocrinol Metab* 2006;19:987–993.
- 10 Bondy CA, Turner Syndrome Study Group: Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007; 92:10–25.
- 11 Carel JC, Mathivon L, Gendrel C, Ducret JP, Chaussain JL: Near normalization of final height with adapted doses of growth hormone in Turner's syndrome. *J Clin Endocrinol Metab* 1998;83:1462–1466.
- 12 Saenger P, Wikland KA, Conway GS, Davenport M, Gravholt CH, Hintz R, Hovatta O, Hultcrantz M, Landin-Wilhelmsen K, Lin A, Lippe B, Pasquino AM, Ranke MB, Rosenfeld R, Silberbach M: Fifth International Symposium on Turner Syndrome: recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab* 2001;86:3061–3069.
- 13 Simm D, Degenhardt K, Gerdemann C, Völkl TM, Rauch A, Dörr HG: Chronological age of patients with Turner syndrome at diagnosis. *Klin Paediatr* 2008;220:16–20.
- 14 Massa G, Verlinde F, De Schepper J, Thomas M, Bourguignon JP, Craen M, de Zegher F, François I, Du Caju M, Maes M, Heinrichs C, Belgian Study Group for Paediatric Endocrinology: Trends in age at diagnosis of Turner syndrome. *Arch Dis Child* 2005;90:267–268.
- 15 World Medical Association: The Declaration of Helsinki. 2008; <http://www.wma.net/en/20activities/10ethics/10helsinki/index.html>.
- 16 Greulich WW, Pyle SI: Radiographic Atlas of Skeletal Development of the Hand and Wrist, ed 2. Stanford, Stanford University Press, 1959.

- 17 Marshall WA, Tanner JM: Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303.
- 18 Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P: An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981). *Acta Paediatr Scand* 1991;80:756–762.
- 19 Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA: Cross-sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 1995;73:17–24.
- 20 Ranke MB, Stubbe P, Majewski F, Bierich JR: Spontaneous growth in Turner's syndrome. *Acta Paediatr Scand* 1988;343:22–30.
- 21 Bayley N, Pinneau SR: Tables for predicting adult height from skeletal age: revised for use with the Greulich and Pyle hand standards. *J Paediatr* 1952;40:423–441.
- 22 Reinken L, van Oost G: Longitudinale Körperentwicklung gesunder Kinder von 0 bis 18 Jahren. *Klin Paediatr* 1992;204:129–133.
- 23 Ranke MB, Lindberg A: Turner syndrome within KIGS including an analysis of 1,146 patients grown to near adult height; in Ranke MB, Price DA, Reiter EO (eds): *Growth Hormone Therapy Pediatrics – 20 Years of KIGS*. Basel, Karger, 2007, pp 332–339.
- 24 Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price DA, KIGS International Board. KABI International Growth Study: Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. *J Clin Endocrinol Metab* 2000;85:4212–4218.
- 25 Ranke MB, Linberg, A on behalf of the KIGS International Board: Observed and predicted total pubertal growth during treatment with growth hormone in adolescents with idiopathic growth hormone deficiency, Turner syndrome, short stature, born small for gestational age and idiopathic short stature: KIGS analysis and review. *Horm Res Paediatr* 2011;75:423–432.
- 26 Quigley CA, Crowe BJ, Anglin DG, Chipman JJ: Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *J Clin Endocrinol Metab* 2002;87:2033–2041.
- 27 Sas TC, de Muinck Keizer-Schrama SM, Stijnen T, Jansen M, Otten BJ, Hoorweg-Nijman JJ, Vulmsa T, Massa GG, Rouwe CW, Reeser HM, Gerver WJ, Gosen JJ, Rongen-Westerlaken C, Drop SL: Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: results of a randomized dose-response trial. *J Clin Endocrinol Metab* 1999;84:4607–4612.
- 28 Wasniewska M, De Luca F, Bergamaschi R, Guarneri MP, Mazzanti L, Matarazzo P, Petri A, Crisafulli G, Salzano G, Lombardo F: Early treatment with GH alone in Turner syndrome: prepubertal catch-up growth and waning effect. *Eur J Endocrinol* 2004;151:567–572.
- 29 Antal Z, Karlsson H, Saenger P: Effectiveness of late growth hormone therapy (>12 years CA) in Turner syndrome. *Horm Res* 2009;72(suppl 3):480.
- 30 Wikland KA, Kristrom B, Rosberg S, Svensson B, Nierop AF: Validated multivariate models predicting the growth response to GH treatment in individual short children with a broad range in GH secretion capacities. *Pediatr Res* 2000;48:475–484.
- 31 Cacciari E, Mazzanti L: Final height of patients with Turner's syndrome treated with growth hormone (GH): indications for GH therapy alone at high doses and late estrogen therapy. Italian Study Group for Turner Syndrome. *J Clin Endocrinol Metab* 1999;84:4510–4515.
- 32 Schonau E, Westermann F, Rauch F, Stabrey A, Wassmer G, Keller E, Bramswig J, Blum WF, German Lilly Growth Response Study Group: A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. *Eur J Endocrinol* 2001;144:13–20.
- 33 Ross JL, McCauley E, Roeltgen D, Long L, Kushner H, Feuillan P, Cutler GB Jr: Self-concept and behavior in adolescent girls with Turner syndrome: potential estrogen effects. *J Clin Endocrinol Metab* 1996;81:926–931.
- 34 Lagrou K, Xhrouet-Heinrichs D, Heinrichs C, Craen M, Chanoine JP, Malvaux P, Bourguignon JP: Age-related perception of stature, acceptance of therapy, and psychosocial functioning in human growth hormone-treated girls with Turner's syndrome. *J Clin Endocrinol Metab* 1998;83:1494–1501.
- 35 Reiter EO, Blethen SL, Baptista J, Price L: Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001;86:1936–1941.
- 36 Vanderschueren-Lodeweyckx M, Massa G, Maes M, Craen M, van Vliet G, Heinrichs C, Malvaux P: Growth-promoting effect of growth hormone and low dose ethinyl estradiol in girls with Turner's syndrome. *J Clin Endocrinol Metab* 1990;70:122–126.
- 37 Stahnke N, Keller E, Landy H, Sero Study Group: Favourable final height outcome in girls with Ullrich-Turner syndrome treated with low-dose growth hormone together with oxandrolone despite starting treatment after 10 years of age. *J Pediatr Endocrinol Metab* 2002;15:129–138.
- 38 Costa AM, Lemos-Marini SH, Baptista MT, Morcillo AM, Maciel-Guerra AT, Guerra G Jr: Bone mineralization in Turner syndrome: a transverse study of the determinant factors in 58 patients. *J Bone Miner Metab* 2002;20:294–297.
- 39 Massa G, Heinrichs C, Verlinde S, Thomas M, Bourguignon JP, Craen M, François I, Du Caju M, Maes M, De Schepper J, Belgian Study Group for Pediatric Endocrinology: Late or delayed induced or spontaneous puberty in girls with Turner syndrome treated with growth hormone does not affect final height. *J Clin Endocrinol Metab* 2003;88:4168–4174.
- 40 Soriano-Guillen L, Coste J, Ecosse E, Léger J, Tauber M, Cabrol S, Nicolino M, Brauner R, Chaussain JL, Carel JC: Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. *J Clin Endocrinol Metab* 2005;90:5197–5204.
- 41 Lin TH, Kirkland RT, Kirkland JL: Adult height in girls with Turner syndrome treated with low-dose estrogens and androgens. *Ann Pharmacother* 1994;28:570–571.
- 42 Kastrop KW: Growth and development in girls with Turner's syndrome during early therapy with low doses of estradiol. *Acta Endocrinol Suppl (Copenh)* 1986;279:157–163.