QUALITY OF LIFE AFTER GROWTH HORMONE THERAPY AND INDUCED PUBERTY IN WOMEN WITH TURNER SYNDROME

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Objective To evaluate health-related quality of life (HRQoL) in young women with Turner syndrome (TS) after long-term growth hormone (GH) therapy and induced puberty and to analyze whether HRQoL was influenced by auxologic parameters, pubertal development, or subjective parameters.

Study design The study group comprised 49 women with TS, mean (standard deviation) age 19.6 (±3.0) years, all former participants of 2 GH studies, ≥6 months after GH discontinuation. Puberty was induced by estrogen treatment, at mean age 12.9 (±1.1) years. HRQoL was measured by self-reports of the 2 generic questionnaires, SF36 and TAAQOL. As an additional source of information on HRQoL, we applied parental proxy reports.

Results HRQoL of the women with TS was normal. Remarkably, the women with TS had higher HRQoL scores on some of the scales, including "social functioning" and "role–emotional." Satisfaction with height and breast development had a positive influence on several HRQoL scales.

Conclusions The young women with TS who reached normal height and had age-appropriate pubertal development reported normal HRQoL. The relatively high scores on some of the HRQoL scales can be explained by an estrogen effect or by a possible response shift, indicating a different internal reference in women with TS. We hypothesize that GH and estrogen treatment positively influenced HRQoL in young women with TS. *(J Pediatr 2006;148:95-101)*

See related article, p 102.

It is generally accepted that a main goal of any medical treatment, therapy, or intervention is improving quality of life. The 2 major characteristics of Turner syndrome (TS) are short stature and absence of pubertal development because of gonadal dysgenesis. It is widely held that short children can suffer from physical, social, and psychological problems.[1] Currently, growth hormone (GH) treatment for short stature in children with TS is now an accepted indication in many parts of the world. GH treatment in TS increases growth velocity and normalizes height during childhood and adolescence. This treatment results in a height gain to an adult height within the normal range.[3-6] Another feature of TS is an absence or delay in the development of bodily feminization, which can cause psychosocial problems in affected teenage girls.[2] Age-appropriate induction of puberty with estrogens, which mimics normal pubertal development without compromising adult height, is possible.[4,7]

Several studies have reported psychosocial problems in girls and women with TS, including impaired social relationships, poor self-esteem, and decreased sexual activity.[8-13] Furthermore, these patients are more likely to meet criteria for attention-deficit hyperactivity disorder than controls and are often employed in jobs for which they are overqualified. One study in untreated women with TS assessed their quality of life in terms of working status, daily routine, and love and marriage and reported that most of the unmarried women lived with their parents, that many were well educated and worked as normal women, and that they appeared anxious about their bodies and marriage. Carel et al[14] reported normal HRQoL in GH-treated women with TS, without any influence of height or

DRS	Dose-response study	SES	Socioeconomic status
FRS	Frequency-response study	SDS	Standard deviation score
GH	Growth hormone	SF36	Short Form-36 Health Survey
HRQoL	Health-related quality of life	TAAQOL	TNO/AZL Adult Quality of Life Survey
QoL	Quality of life	TS	Turner syndrome

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other variables associated with GH treatment. This study did not include subjective measures in terms of height, pubertal development, and visible TS features, however.

In the present study we evaluated HRQoL in young women with TS after long-term GH treatment and puberty induction at an age-appropriate time. We compared HRQoL scores of the young women with TS to scores in samples from the general population. We also analyzed whether HRQoL outcome was influenced by anthropometric parameters, pubertal development, and subjective parameters, such as satisfaction with height and breast development.

METHODS

Subjects

All young women with TS who had participated in 2 earlier GH trials were invited to participate in an HRQoL evaluation. The 2 earlier trials were a dose-response GH trial (DRS) and a frequent-response GH trial (FRS) to investigate the effects of long-term GH therapy, given in different dosages and at varying frequencies (see below). To be eligible, a woman had to have discontinued GH treatment for at least 6 months and to be able to fill in the questionnaires. Forty-nine women agreed to participate (response rate 49/69: 71%), with 20 women not participating either for practicality reasons or because they had lost interest in participating in such studies.

GH Trials

The study designs of the DRS and the FRS have been described by Sas et al.[3,15] Both of these studies started in 1989. Sixty-nine cases were eligible for participation in the HRQoL evaluation, including 52 from the DRS and 17 from the FRS.

Dose-Response Study

Sixty-eight Dutch girls with TS, age 2 to 11 years, were enrolled in the open randomized multi-center GH DRS. Biosynthetic GH (r-hGH Norditropin; Novo Nordisk A/S, Denmark) was given subcutaneously once daily at bedtime at a dose of 1.3, 2, or 2.7 mg/m^2 body surface area/day (~0.045, 0.067, or 0.09 mg/kg/day). To induce puberty, micronized 17β-estradiol was given to the girls age 12 years and older after at least 4 years of GH treatment. During the first 2 years, 5 μg/kg body weight/day was given orally, followed by a dose of 7.5 μg/kg/day in the third year and 10 μg/kg/day thereafter. Cyclic progestogen therapy (duphaston, 5 mg/day for the first 14 days of each month) was added after 2 years of estrogen therapy. If puberty had developed spontaneously (as marked by Tanner breast stage ≥ 2) during the study period and before the start of estrogen therapy, then no estrogen was given during GH therapy. Of the 68 subjects, 6 girls dropped out of the study and were lost to follow-up, 6 girls were still receiving GH treatment, and 4 girls were unable to complete the questionnaires because of mental retardation. This left 52 girls eligible for participation in the HRQoL evaluation; 34 agreed to participate.

Frequency-Response Study

Nineteen Dutch girls with TS, age 11 years and older, were enrolled in an open randomized multicenter FRS. Biosynthetic GH (r-hGH Norditropin; Novo Nordisk A/S, Denmark) was given subcutaneously once or twice daily in a dose of 2 mg/m^2 body surface area/day (~0.067 mg/kg/day). To induce puberty, ethinyl estradiol was given orally at a dose of 0.05 μg/kg body weight/day at start of the trial. After the first 2.25 years of GH treatment, the ethinyl estradiol dose was increased to 0.10 μg/kg/day, and cyclic progestogen therapy was added. Two girls were unable to fill in the questionnaire because of mental retardation, leaving 17 girls eligible for participation in the HRQoL evaluation; 15 agreed to participate.

Health-Related Quality of Life Evaluation

The HRQoL evaluation was performed after GH treatment had been discontinued for at least 6 months and final height had been reached. The HRQoL evaluation consisted of 2 generic self-report questionnaires, the Medical Outcome Study Short Form-36 Health Survey (SF36) and the TNO/AZL Adult Quality of Life (TAAQOL). As an additional source of information on QoL of the study population, we applied proxy reports. The women were used as proxies because women with TS are considered more immature than their peers.[10]

SF36

We used the validated Dutch translation of the SF36 questionnaire.[16] Developed by Ware and Sherbourne in 1992,[17] the SF36 measures physical and mental health and social functioning. It is a self-report questionnaire consisting of 35 items divided into the following 8 domains (with the number of items in each domain in parentheses): physical functioning (10), role limitations due to physical health problems (4), bodily pain (2), general health perceptions (5), vitality (4), social functioning (2), role limitations due to emotional health problems (3), and mental health (5). For each domain, the results were scored from 0 to 100, with a higher score indicating a better subjective quality of life.

TAAQOL

The TAAQOL explicitly offers respondents the ability to differentiate their ability to function and their associated feelings. This concept, known as HRQoL, qualifies the quantity of the problem with its emotional impact. The TAAQOL was designed in the Netherlands and validated in the general population.[18,19] It is a self-report questionnaire consisting of 45 items that refer to the preceding few weeks, divided into the following 12 domains (with the number of items in each domain in parentheses): gross motor skills (4), fine motor skills (4), cognition (4), sleep (4), bodily pain (4), social functioning (4), daily activities (4), sexual functioning (2), vitality (4), positive emotions (4), negative passive emotions (eg, depression) (4), and negative active emotions (eg, aggression) (3). For each

domain, the results are scored from 0 to 100, with higher scores indicating a better subjective quality of life. An example of the format of the questionnaire is shown in the Figure, available at www.jpeds.com.

Reference Population

SF36 and TAAQOL data of the Dutch general female population are available and were used for comparison. The population for the female reference data for the SF36 had an age range of 16 to 25 years (n = 121),[16] and that for female reference data for the TAAQOL had a mean age of 19.7 (2.0) and a range of 16 to 22 years (n = 116).[18]

Additional Measurements

The mailed questionnaires contained additional items on subjective parameters of nationality and socioeconomic status (SES). Information provided by the parents included parent's occupation, parent's educational level, daughter's nationality, and daughter's current and past health problems. The SES scores ranged from 1 to 3. When both parents were employed, the highest of their 2 SES scores was used. For unemployment, the lowest SES score was used.[20] Reported health problems were counted.

Both the women with TS and their parents answered the following questions about the women with TS:

- Are you satisfied with your (your daughter's) adult height?
- Are you satisfied with your (your daughter's) breast development?
- Do you think that other people can see that you (your daughter) have (has) Turner syndrome?
- If answered yes to the previous question, how do you think people can see that you (your daughter) have (has) Turner syndrome?
- Do you think your/your daughters' appearance will cause limitations? If "yes," which limitations?

Furthermore, they were asked where the woman with TS was living, with parents or elsewhere.

The following variables were scored dichotomously (0 = no, 1 = yes): being satisfied with height and breast development, having visible features of TS, and having self-reported limitations due to physical appearance. In addition, the following spontaneously reported limitations due to physical appearance were also scored dichotomously (0 = no, 1 = yes): limitations in relationships, limitations in job perspectives, feelings of insecurity, lacking charisma, and difficulty buying shoes or clothes. To determine whether the quantity of self-reported features of TS had a linear effect or a dichotomous effect, the self-reported visible features of TS were counted and scored from 0 to 3, with 0 representing no visible features and 3 representing 3 or more visible features.

Statistical Analysis

All data are expressed as mean (standard deviation) unless otherwise specified. Independent *t*-tests were used to test for differences between self-reports or parent reports and the normal references based on a review of HRQoL measures of the TAAQOL and SF36 scales. Independent *t*-tests were also used to test for differences between participants and nonparticipants to the HRQoL study. A paired *t*-test was used to test for differences between self-reports and parent reports. The McNemar test and the Wilcoxon signed-rank test were used to test for differences in reported subjective data on features of TS and limitations between the women with TS and their parents.

The effect of physical features of TS and limitations on HRQoL outcome, reported by the patients with TS was analyzed per HRQoL scale in a regression model. Each of the following explanatory variables was entered separately in the model, along with age and SES: satisfaction with height, satisfaction with breast development, visible features of TS, self-reported limitations (ie, limitations in relationships, limitations in job perspectives, and feelings of insecurity), number of health problems, age at start of puberty, height standard deviation score (SDS) gain, and adult height. Age at start of puberty was defined as age (years) at first visit with Tanner breast stage B2,[21] spontaneous or induced. Height was scored in cm.

Results from the regression analyses are given as unstandardized coefficients (B) along with their 95% confidence intervals and 2-tailed *P* values. The estimated B coefficient is the relevant effects adjusted for age and SES. Only B coefficients with *P* value < .15 and only variables with a significant influence on at least 1 of the HRQoL scales are reported. The effects of age and SES are not presented. *P* values < .05 were considered significant. All calculations were performed with SPSS 11.5 software.

Ethical Considerations

Our institution's Medical Ethics Committee (MEC) of each participating center approved earlier GH trials and the MEC of our institution the subsequent HRQoL evaluation. Written informed consent was obtained from the parent or custodian of each child for the GH study and from each participant for the HRQoL evaluation.

RESULTS

Table I presents the clinical characteristics of the 49 women with TS who participated in the HRQoL evaluation. The average height of 160.7 (6.5) cm is −1.2 (1.1) SDS lower than the normal Dutch references[22] and 2.2 (1.0) SDS higher than North European untreated women with TS.[23] The mean age at onset of puberty was 12.9 years, compared with 10.8 years in the normal population.[7,24] The progression through puberty, defined as the time intervals from breast stages B2 to B3, B2 to B4, and B2 to B5, was comparable to that of normal references (data not shown).[7] Three of the 49 participating women with TS (6%) experienced a spontaneous start of puberty. All of the 49 women were receiving hormone replacement therapy in adult dosages. The duration of GH treatment was 7.1 (±2.7) years. At the time of the HRQoL evaluation, the mean time after GH discontinuation was 2.9 (±1.6) years.

Table I. Clinical data for young women with TS who participated in the HRQoL evaluation

	TS population (n = 49)
Age (years) at HRQoL evaluation	19.6 (3.0)
Range (yrs)	14.8-25.8
Adult height (cm)	160.7 (6.5)
Adult height SDS*	−1.2 (1.1)
Height SDS gain†	1.7 (1.0)
Age at onset of puberty (years)	12.9 (1.1)
Karyotype	
45,X	39 (80%)
Other	10 (20%)
Living situation	
With parents	39 (85%)
With partner	2 (4%)
On own	5 (11%)

Data are expressed as mean (±SD) or n (%).
*Height for age: references for healthy Dutch girls.[22]
†Final height SDS – height SDS at the start of GH therapy (references for untreated TS girls[23]).

No significant differences in breast development or other clinical characteristics as listed in Table I were found between the women who participated in the HRQoL evaluation and those who did not participate.

SF36

Table II gives the HRQoL results of the SF36 of young women with TS. The women with TS reported a significantly better HRQoL in the "social functioning," "role limitations–emotional," and "bodily pain" domains compared with the normal population. For the remaining domains, the HRQoL scores were equal to those of the normal population.

TAAQOL

The TAAQOL (Table III) revealed significantly better HRQoL scores for "pain," "daily activities," "sexuality," and "aggressive emotions" in the women with TS compared with normal references. For the remaining domains, the HRQoL scores were comparable between the 2 populations. For the "social functioning" domain, the self-reports and the parent reports were significantly different in terms of HRQoL.

ADDITIONAL DATA

Of the women with TS, 26% had a low SES level, 34% had an intermediate SES level, and 40% had a high SES level, not significantly different from the SES levels in the normal population (ie, 33% low, 34% intermediate, and 33% high).[20]

Table IV gives data for subjective measures reported by the TS patients and their parents. Four of the women with TS and 2 of the parents did not return the questionnaire. The 3 patients who were not happy with their height would have liked to be taller. Of the 17 patients who were not happy with their breast development, 3 (18%) judged their breasts of uneven size, 5 (29%) judged them too small, and 9 (53%) judged them too big. The parents scored significantly fewer features of TS than their daughters. The most common features of TS reported by the women with TS were short stature (n = 12), neck webbing (n = 8), and pigmented nevi (n = 4). Also reported were abnormal nails, characteristic facial expression, and slower motor performance.

The frequency of medical problems reported by the parents of the women with TS is 0 in 3 cases (7%), 1 in 12 cases (27%), 2 in 15 cases (33%), 3 in 10 cases (22%), and 4 in 5 cases (11%). Two respondents did not answer this question.

Factors Influencing HRQoL Outcome

The explanatory variables that were evaluated separately are listed in Table V (available at www.jpeds.com). The estimated B coefficients, the relevant effects adjusted for age and SES, are also given. The table shows that the women who where satisfied with their height had a significantly better HRQoL (approximately 25 on a scale of 0 to 100) on the physical performance scales of both SF36 and TAAQOL. The height SDS gain had a significant positive effect on the HRQoL outcome of "role limitations due to physical health problems," with an 8.3-point higher HRQoL score per unit of SDS height gain. SDS height gain also positively influenced daily activities. The absolute height only significantly influenced the HRQoL outcome of "vitality" of the TAAQOL. The women who had feelings of insecurity due to their physical appearance had a lower HRQoL in the "social functioning" domain. The difference was 18.5 points (95% confidence interval [CI] = 2.2 to 34.8) according to the SF36 and 30.6 points (95% CI = 13.5 to 47.7) according to the TAAQOL. Remarkably, age at onset of puberty did not significantly influence any of the HRQoL outcomes. However, the satisfaction with breast development at time of the HRQoL evaluation did influence several of the HRQoL scales.

Having visible features of TS had a significant positive effect on scores for the "pain" domain of the TAAQOL (Table V). This indicates that having reported visible features of TS is associated with a higher HRQoL with respect to pain, but the *quantity* of the reported visible features of TS was of no affect (data not shown).

SES significantly positively influenced scores in the "depressive emotions" domain of the TAAQOL (data not shown). Karyotype, reported number of medical problems in the past, and age at onset of puberty had no significant influence in either of the HRQoL instruments. The SF36 HRQoL domains "vitality," "mental health," "general health," and "role–emotional" were not significantly influenced by the tested variables. Furthermore, for the TAAQOL HRQoL domains "cognition," "positive emotions," "depressive emotions," and "aggressive emotions" were not influenced by the variables evaluated.

DISCUSSION

The women with TS reported higher HRQoL scores in the domains "social functioning" and "role limitations due to

Table II. HRQoL results for the SF36

Domain	Self-report (n = 48)	Parent-report (n = 35)	Reference* (n = 121)	Self-report vs reference (*P* value)	Self-report vs parent report (*P* value)
Physical functioning	91.3 (12.4)	90.0 (17.8)	92.2 (11.0)	.630	.545
Role-physical	91.1 (20.3)	92.1 (22.5)	86.8 (28.3)	.145	.711
Bodily pain	86.4 (16.3)†	91.1 (20.0)†	79.0 (20.0)	.003	.425
Vitality	68.0 (18.0)	71.7 (13.5)	68.0 (16.2)	.994	.460
General health	79.0 (16.3)	74.3 (19.9)	76.3 (16.6)	.253	.317
Social functioning	92.4 (15.2)‡	90.4 (17.4)	86.7 (16.9)	.012	.090
Role–emotional	90.3 (24.8)†	91.4 (26.0)‡	79.2 (33.5)	.003	.447
Mental health	77.2 (17.0)	79.0 (12.8)	75.8 (14.4)	.580	.907

Results are expressed as mean (±SD); the higher the score, the better the HRQoL.
*From.[16]
†$P < .01$ compared with reference values.
‡$P < .05$ compared with reference values.

Table III. HRQoL results of the TAAQOL

Domain	Self-report (n = 49)	Parent-report (n = 36)	Reference* (n = 116)	Self-report vs reference (*P* value)	Self-report vs parent report (*P* value)
Gross motor functioning	92.6 (15.0)	90.3 (21.0)	89.3 (19.6)	.299	.617
Fine motor functioning	98.5 (5.3)	96.0 (8.9)	95.7 (13.1)	.054	.075
Cognitive functioning	79.7 (23.7)	84.2 (19.2)	83.2 (21.2)	.356	.092
Sleep	78.2 (23.2)	75.5 (26.9)	71.7 (25.7)	.129	.853
Pain	86.6 (16.7)†	85.9 (18.7)‡	76.7 (21.7)	.005	.862
Social functioning	90.3 (17.6)	85.1 (15.9)§	89.3 (17.4)	.731	.001
Daily activities	91.1 (16.4)†	85.8 (23.2)	82.6 (22.8)	.008	.144
Sexuality	98.9 (5.3)†	92.1 (21.9)	89.8 (21.7)	< .001	.105
Vitality	63.9 (20.4)	68.6 (20.0)	62.1 (22.6)	.630	.385
Positive emotions	69.6 (17.9)	69.4 (15.9)	73.3 (20.7)	.275	.804
Depressive emotions	78.1 (18.1)	78.7 (16.5)	75.1 (19.0)	.351	.709
Aggressive emotions	90.9 (13.5)†	89.8 (9.0)†	82.7 (17.8)	.002	.353

Results are expressed as mean (±SD); the higher the score, the better the HRQoL.
*From.[18]
†$P < .01$ compared with reference values.
‡$P < .05$ compared with reference values.
§$P = .001$, self-reports compared with parent reports.

emotional health problems." This means that women with TS felt less restricted in social contacts and/or daily life due to their physical health or emotional problems than the reference population. The reported results of better HRQoL in social functioning in the women with TS is remarkable; earlier data indicated that women with TS scored significantly lower on social acceptance scales than the normal population.[8,25] But the present study indicates that HRQoL is not influenced by this factor, as the women with TS reported normal or even better HRQoL in terms of social functioning.

A possible explanation for this finding is that the women with TS no longer feel different from their peers as they attain normal height and normal feminization during the growth phase and adulthood. Satisfaction with breast development and a lack of feelings of insecurity due to physical appearance have a significant positive influence on social functioning. These data emphasize the importance of feeling equal to normal peers. GH and estrogen treatment resulted in normal height and breast development in most of the girls[4,7] and diminished differences from peers. Because short stature and delayed pubertal development can be of significant negative influence on HRQoL,[1,2] we hypothesize that GH treatment and appropriate induction of puberty can normalize HRQoL in women with TS.

Our group of women with TS showed even a *better* HRQoL than the reference population on some of the HRQoL scales. The women with TS had less aggressive feelings, demonstrating significantly better HRQoL for the TAAQOL domain "aggressive emotions." These results confirm earlier reports that girls with TS have less delinquent and aggressive behavioral problems.[8,9] This might be an effect of estrogen treatment, because estrogens significantly decrease aggressive

Table IV. Additional data reported by women with TS and their parents

	TS women (n = 45)	Parents (n = 47)	*P* value
Satisfied with height:			
Yes	42 (93%)	44 (94%)	1.00
No	3 (7%)	3 (6%)	
Satisfied with breasts:			
Yes	26 (58%)	27 (57%)	.77
No	17 (38%)	18 (38%)	
No opinion	2 (4%)	2 (4%)	
Self-reported visible			
TS features: None	12 (26%)*	28 (61%)	.007
Yes: 1	21 (46%)	11 (24%)	
2	11 (24%)	6 (13%)	
≥3	2 (4%)	1 (2%)	
Self-reported limitations due to physical appearance: None	35 (78%)	30 (67%)†	
Yes:	10 (22%)	15 (33%)	.66
- Relationships	3*‡	1	.024
- Work	4	3	.36
- Feelings of insecurity	4‡	3	.32
- Lack of charisma	-	6	.16
- Buying clothes/shoes	-	2	1.00

Data are expressed as n (%).
*Significant difference between the TS women and their parents.
†Two parent reports were missing.
‡Two limitations reported by 1 patient.

and delinquent behavior in girls with TS,[9] whereas GH has no influence.[26] It also may be influenced by the diminished androgen levels in TS,[27] caused by lack of ovarian androgen production, because androgens increase aggressiveness.[28] However, the higher percentage of patients with karyotype 45,X in our study in comparison with other studies (approximately 80% vs 65%) also must be taken into account. Spontaneous puberty, indicating (some) ovarian function, is less common in patients with karyotype 45,X than in patients with mosaic karyotype.

As a group, the women with TS had normal HRQoL for motor performance. The women with TS who were satisfied with their height and those with a greater height gain had a better HRQoL in areas of physical/motor functioning, suggesting a positive effect of the GH-induced height gain. The effect of estrogen treatment also may contribute to this finding, because estrogens also improve motor performance and speed in women with TS.[29,30]

The possibility exists that the women with TS have undergone a "response shift," a change in internal standards or values.[31] This phenomenon has been reported in elderly persons who exclude some age-related problems or morbidities when they self-assessed their susceptibility to illness.[32] In terms of the present study, response shifting in our subjects may mean that the women with TS have different internal references than normal women. Facts supporting this hypothesis can be found not only in the reported relatively better HRQoL for "social functioning" and "role–emotional," but also in the better HRQoL for "pain" and "sexuality." Based on our previous research and on reports in the literature, we did not expect these results. Because women with TS have more medical problems than the normal population, they tend to experience more pain and discomfort than those other women; also, women with TS are reported to be less sexually active than their normal peers.[12] Thus we remain uncertain whether the relatively high HRQoL scores for these domains in our women with TS reflects actual health effects or result from response shifting. Future studies that include cognitive interviewing will aid investigation of this hypothesis.

In general, the parent reports yielded results similar to those reported by their daughters with TS, except for assigning lower scores for their daughter's social functioning on the TAAQOL questionnaire (see Results). This finding confirms the validity of the HRQoL outcomes reported by the women with TS. The parents of daughters with TS can be considered first-choice proxy raters because they typically have intensive contact with their daughters, a phenomenon often seen in young adults with chronic diseases or disabilities and their parents.

Age at onset of puberty was of no significant influence on several HRQoL outcomes. Absolute height negatively influenced "vitality;" however, the effect was small (B = −1.1; range, −2.0 to −0.2). The normal height and pubertal development of our study population, as well as the small differences in final height and age range of pubertal onset, may explain the lack of a significant affect of these measures on HRQoL. These results confirm the recently published findings of Carel et al[14] that indicate normal HRQoL in TS with no significant influence of GH treatment-related variables, such as adult height or estimated height gain. However, our data reveal a significant influence of height gain on the "role limitations due to physical health problems" and "daily activities" domains. Furthermore, in our study, satisfaction with height and/or breast development had a significant positive influence on several HRQoL domains, and those women with TS who reported feelings of insecurity due to their physical appearance had lower HRQoL in the "social functioning" domain.

To appreciate our results one has to consider the following. HRQoL was not evaluated longitudinally, because the HRQoL questionnaires were developed in the early and mid-1990s and the GH studies began in 1989, before HRQoL became recognized as an important measure of the impact of a specific disorder, disease, or therapeutic outcome. Secondly, our study did not specifically evaluate the consequences of infertility on HRQoL. This might be a relevant factor with increasing age, because infertility is present in the majority of adults with TS and can have a significant influence on HRQoL.[33-36] Future studies are needed to evaluate the influence of infertility on HRQoL in women with TS. Finally, it would have been ideal to compare the treated TS population with an untreated TS population. However, given that GH treatment for girls with TS has been common practice since the early 1990s, no untreated population in the same

age range was available for study. Finally the response rate was 71%. There might have been a selection bias, but we believe that this is unlikely, because there were no significant differences in clinical data, such as age, height, height gain, age at onset of puberty and karyotype, between the respondents and nonrespondents.

In conclusion, our study shows a normal health related quality of life in young women with Turner syndrome after long-term GH treatment and puberty induction at an age-appropriate time. The relative high scores on some of the HRQoL-scales can be explained by an estrogen-effect or by a possible response shift, indicating that the TS women might have a different internal reference. Additionally, satisfaction with height and with breast development had a significant positive influence on several HRQoL scales, including social functioning and physical functioning. Therefore we hypothesize that GH and estrogen treatment positively influenced HRQoL in young women with TS.

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