

# Self-Esteem and Social Adjustment in Young Women with Turner Syndrome—Influence of Pubertal Management and Sexuality: Population-Based Cohort Study

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**Context:** Pediatric management of patients with Turner syndrome focuses on height, frequently resulting in a delay of pubertal induction. The influence of pubertal management on psychosocial adjustment and sex life has not been evaluated in Turner syndrome patients.

**Objective:** The objective of the study was to identify the determinants of self-esteem, social adjustment, and initiation of sex life in patients with Turner syndrome, particularly those related to pubertal management.

**Design:** This was a prospective evaluation, the StaTur study.

**Setting:** The study was conducted with a population-based registry of GH-treated patients.

**Participants:** Participants included 566 young adult women with Turner syndrome, aged  $22.6 \pm 2.6$  yr (range, 18.3–31.2).

**Main Outcome Measures:** Measures used in the study were Coopersmith's Self-Esteem Inventory, Social Adjustment Scale Self-

Report, questions on sexual experience, and extensive data on pediatric management.

**Results:** Low self-esteem was associated with otological involvement and limited sexual experience. Low social adjustment was associated with lower paternal socioeconomic class and an absence of sexual experience. Late age at first kiss or date was associated with cardiac involvement and a lack of spontaneous pubertal development. Age at first sexual intercourse was related to age at puberty and paternal socioeconomic class. Delayed induction of puberty had a long-lasting effect on sex life. Height and height gain due to GH treatment had no effect on outcomes.

**Conclusions:** Puberty should be induced at a physiologically appropriate age in patients with Turner syndrome to optimize self-esteem, social adjustment, and initiation of the patient's sex life. Therapeutic interventions altering normal pubertal development in other groups of patients should be reconsidered in light of these findings. (*J Clin Endocrinol Metab* 91: 2972–2979, 2006)

TURNER SYNDROME AFFECTS 1 in 2500 females and results from the total or partial absence of one of the X chromosomes (1–3). The principal features of Turner syndrome are short stature, dysfunctional gonads, cardiac and renal malformations, otological problems leading to hearing impairment, and dysmorphic features of various severities. Treatment has focused on height (4). GH treatment increases adult height, as shown by a randomized controlled study (5), confirming earlier reports (6, 7). However, the height gain is quite variable and its clinical significance is a matter of debate (8). Pubertal development must be induced by drug treat-

ment in girls with Turner syndrome presenting primary ovarian failure. Many studies have considered the effects of this management of puberty on height (9, 10), but little is known of its effects on the initiation of sexual activity and its impact on psychosocial functioning.

As for all chronic diseases of childhood, the medical treatment of Turner syndrome should aim to reduce the impact of this condition on psychosocial functioning, in both childhood and adulthood. However, the impact of management on psychosocial outcomes has not been systematically evaluated for Turner syndrome. In a previous study, we observed that health-related quality of life was similar in adult women with Turner syndrome treated with GH in childhood and the general population (11). We identified several components of the disease or consequences of medical management as factors associated with low health-related quality of life scores: cardiac and otological involvement, induction of puberty after the age of 15 yr, and higher expectations from

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Abbreviations: BMI, Body mass index; CI, confidence interval; GHQ-12, General Health Questionnaire 12; HR, hazard ratio; SAS-SR, Social Adjustment Scale Self-Report; SDS, SD score; SEI, Self-Esteem Inventory.

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GH treatment. In contrast, height or height gain from treatment had no influence (11). Other aspects of psychosocial functioning, such as self-esteem and social adjustment, have not been systematically evaluated in patients with Turner syndrome (12–15). It is therefore important to analyze the influence of management options in childhood on these dimensions to help pediatricians make the best choices concerning the management of their patients.

The factors determining the onset of sexuality in humans are poorly characterized, and attention has mostly focused on behavioral, environmental, and psychosocial determinants (16). The timing of puberty affects the onset of sexuality in the general population (16–18). Several medical interventions affect the timing of puberty, but their effects on sexual behavior have not been studied (19, 20). Estrogen replacement in hypogonadal girls has a modest short-term effect on sexual behavior (21). Therefore, Turner syndrome, in which puberty is medically induced in most cases, provides a model to investigate the influence of the timing of puberty on the onset of sexuality.

In this study, we evaluated self-esteem, social adjustment, and sexuality, together with their determinants, in a population-based cohort of Turner syndrome patients treated with GH in France.

## Patients and Methods

The design of the study has been described in detail elsewhere (9, 11). The StaTur cohort includes all patients with a diagnosis of Turner syndrome diagnosed 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. The study was approved by the Département de la Recherche Clinique et du Développement of Assistance Publique-Hôpitaux de Paris and was considered as requiring no informed consent because on-treatment data had been collected as part of a national mandatory program, and patients were free to respond to the questionnaire. The Association France-Hypophyse database is nominative, which allowed mailing the questionnaires. A coded identifier was included to medical data exported to the study database and the questionnaires. Data from the questionnaire were entered in the database with the coded identifier but without the personally identifying information, allowing us to keep this confidential information anonymous. The patients were informed that the database and data analysis were anonymous, although the questionnaires included a coded link to their identity and clinical data.

### Data collected

Data relating to features associated with Turner syndrome, growth, and treatments were collected throughout childhood and adolescence (9, 22). In 2001, a postal questionnaire was sent to all patients older than 18 yr on March 31, 2001. This survey included the Coopersmith's Self-Esteem Inventory (SEI) (23) and the Social Adjustment Scale Self-Report (SAS-SR) (24) in addition to the quality of life questionnaire Short Form 36 of the Medical Outcome Study and the General Health Questionnaire 12 (GHQ-12), a measure of psychological distress (11, 25). It also dealt with demographic characteristics, current health status (morbidity, medication), sexual experience, and expectations from GH treatment. The SEI contains 58 trait-descriptive sentences to which subjects respond by indicating whether the sentences describe them. Scoring is based on a 26-item general subscale and on three 8-item subscales evaluating self-esteem in the social, family, and working areas. The total SEI score is the sum of the four subscales and ranges between 0 and 50. Higher scores indicate higher self-esteem. The SAS-SR questionnaire consists of 54 questions measuring instrumental and communicative role performance over the past 2 wk. It includes questions on work, social and leisure activities, relationships with family, marital partner, children,

and perception of economic functioning. Each item is scored on a 5-point scale with higher scores indicating lower social adjustment.

Sexual experience was assessed by means of several questions, asking whether the young women had experienced kissing or dating and had had sexual intercourse (yes/no and age at the first time), from which we constructed two categorical variables. The first, called lifetime sexual experience, classified women as having: 1) no experience of kissing or dating; 2) kissing or dating experience but no experience of intercourse; 3) experience of sexual intercourse but no experience of living with a male partner; or 4) experience of sexual intercourse and currently living with a male partner. The second variable, sexual intercourse experience at the age of 20 yr, took into account the age of participants (with its obvious effect on sexual experience). Because normative national data indicate that 85% of women have experienced sexual intercourse by the age of 20 yr (26), we divided participants into three categories: 1) those who had had sexual intercourse before the age of 20 yr; 2) those over the age of 20 yr who had not had sexual intercourse before the age of 20 yr; and 3) women under the age of 20 yr with no experience of sexual intercourse, for whom no conclusion can be drawn. To evaluate the potential influence of the center at which patients had been followed up, we categorized them according to their size (large,  $n = 6$ , 188 patients; medium,  $n = 12$ , 181 patients; and small,  $n = 94$ , 197 patients). Body mass index (BMI) at the time of the questionnaire or adult height measurement was categorized in three tertiles ( $<20.5$ ,  $20.5$ – $25$ ,  $> 25$  kg/m<sup>2</sup>) and expressed in SD score (SDS) using national normative data (27).

### Statistical analysis

We quantified the relationships between subscores for the SEI and SAS-SR questionnaires, clinical and demographic characteristics, and sexual experience by means of univariate linear regression. Variables identified as significant in this univariate analysis were then included in a multiple regression model with a backward selection procedure (28).

Sexuality was analyzed by means of survival analysis, using first kiss or date or first sexual intercourse as the event considered. Given that events had not occurred in all women, we used age at time of the survey as censored time for these observations. Survival curves were derived from Kaplan-Meier estimates (29). Multivariate analyses used the Cox proportional hazards regression model (30), with a backward stepwise selection procedure. We defined  $P < 0.05$  as statistically significant. Calculations were performed with SAS software (SAS Institute Inc., Cary, NC).

## Results

### Characteristics of the participants

The flow chart describing enrollment of patients is presented in Fig. 1. As described previously, participants ( $n = 566$ ) and nonparticipants ( $n = 325$ ) were similar in all characteristics except for adult height, participants being a mean of 2.7 cm taller than nonparticipants (11). Details on GH treatments and height outcomes have also been described earlier (9, 11). Medical and demographic characteristics and scores for the SEI and SAS-SR subscales are presented in Table 1. Women with Turner syndrome had low SEI scores, particularly for the general and social scales. Pubertal onset was defined as the time of spontaneous breast development or initiation of sex steroid treatment. Pubertal onset was medically induced in 405 patients at  $14.9 \pm 1.0$  yr and spontaneous in 127 (missing data in 34). Of these 127 patients, 61 required sex steroids later, for pubertal development to complete. The mean BMI was  $23.5 \pm 4.3$  kg/m<sup>2</sup> or  $1.0 \pm 1.6$  SD score.

### Self-esteem and its determinants

Five of the 38 variables tested were retained in the multivariate models (Table 2). Women with a high GHQ-12 score

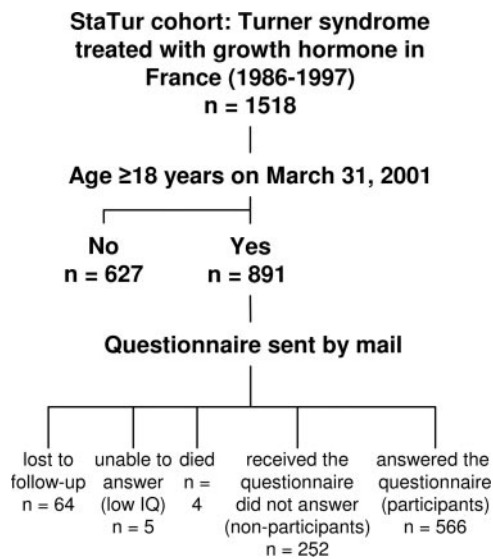


FIG. 1. Flow chart of patient enrollment.

had low self-esteem, as estimated from all SEI components. Otological abnormalities were associated with low self-esteem in all but one dimension (work). Lifetime sexual experience was associated with the overall SEI scale and two of the four SEI subscales, with scores increasing with sexual experience. Earlier menarche was associated with lower self-esteem for the work dimension only, but age at onset of puberty (B2 stage) was not a predictor of SEI scores. Patients in the highest BMI tertile group had a lower general SEI score, compared with those of the middle BMI tertile group. Several variables were not associated with SEI scores. These variables included karyotype, participant's professional situation, age at which the questionnaire was completed, height or parameters associated with GH treatment, genital malformations in patients with a 45,X/46,XY karyotype, size of the center, type of estrogen used, and delay to progestin treatment.

#### Social adjustment and its determinants

Eight of the 38 potentially explanatory variables tested were retained in the multivariate models (Table 3). As expected, socioeconomic variables influenced social adjustment. Older participants had lower scores on the family scale. Categorical GHQ-12 score was correlated with all dimensions of social adjustment. Otological involvement had a minor effect. Lifetime sexual experience was associated with overall and social-leisure SAS-SR scale scores. In contrast to what was observed with the SEI scale, increasing sexual experience had no effect, suggesting an all-or-nothing effect of kissing or dating. Interestingly, women over the age of 20 yr at the time of the survey who had never had sexual intercourse or who had begun their sex lives late had higher scores on the work scale. Several variables were not associated with SAS-SR scores. These variables included adult height or estimated height gain, dysmorphic features, age at menarche, karyotype, cardiac involvement, genital malformations, size of the center, type of estrogen used, and delay to progestin treatment.

TABLE 1. Characteristics of studied patients

Age at time of study (yr) [range]	22.6 ± 2.6 [18.3/31.2]
Socioeconomic status	
Paternal socioeconomic class	
Retired - inactive	132 (23)
Manual worker	129 (23)
Nonmanual worker	305 (54)
Participant's educational level	
Age < 20 yr	203 (36)
Did not graduate from high school	144 (25)
High-school graduation and higher	219 (39)
Professional situation	
Professional activity	163 (29)
Unemployed	120 (21)
Student	283 (50)
Turner syndrome characteristics	
Dysmorphic features	276 (49)
Otological involvement	148 (26)
Cardiac involvement	71 (13)
Type of pubertal development	
Spontaneous	66 (12)
Spontaneous with secondary sex steroid treatment	61 (11)
Induced	405 (72)
Sexuality	
Lifetime sexual experience	
Intercourse experience and living with male partner	42 (8)
Intercourse experience	172 (30)
Kissing or dating experience	165 (29)
No experience	187 (33)
Sexual experience at 20 yr	
Not evaluable	80 (14)
No	354 (63)
Yes	132 (23)
GHQ-12 score ≥ 3	
No	428 (76)
Yes	138 (24)
SEI scale <sup>a</sup>	
General	17.5 ± 5.3 (−1.3 ± 1.5 SDS) <sup>b</sup>
Familial	6.5 ± 1.8 (−0.3 ± 1.1 SDS) <sup>b</sup>
Social	5.7 ± 1.8 (−0.8 ± 1.4 SDS) <sup>b</sup>
Work	6.3 ± 1.6 (−0.3 ± 1.3 SDS) <sup>b</sup>
Overall	36.0 ± 8.9 (−1.1 ± 1.5 SDS) <sup>b</sup>
SAS-SR scale <sup>c</sup>	
Family	1.6 ± 0.5
Social, leisure	1.9 ± 0.6
Work	1.4 ± 0.5
Economic	1.3 ± 0.7
Overall	1.7 ± 0.4

Results are shown as means ± SD or numbers (%). The sum of percentages may be not equal to 100% because of missing data.

<sup>a</sup> SEI scores were converted into SDS using reference values from Ref. 45.

<sup>b</sup>  $P < 0.001$  for comparison with reference values.

<sup>c</sup> Given the small number of participants with a partner or children, the corresponding SAS-SR scores were not analyzed.

#### Sexuality

Because sexuality was found an important determinant of self-esteem and social adjustment, we constructed Kaplan-Meier curves for the occurrence milestones in the development of sexuality (Figs. 2 and 3). In univariate analysis, age at first kiss or date was associated with age at the onset of puberty, induced *vs.* than spontaneous puberty, and ocular or cardiac involvement. In the final multivariate Cox model, induced (as opposed to spontaneous) puberty [hazard ratio

**TABLE 2.** Determinants of self-esteem

Dimension	Self-esteem (higher scores indicate higher self-esteem)					% Variance of the overall score explained
	General	Familial	Social	Work	Overall	
Range of values	<b>[0–26]</b>	<b>[0–8]</b>	<b>[0–8]</b>	<b>[0–8]</b>	<b>[0–50]</b>	
r <sup>2</sup>	<b>0.19</b>	<b>0.15</b>	<b>0.11</b>	<b>0.14</b>	<b>0.20</b>	
Participant's educational level						
Age <20 yr				–0.11 ± 0.15		
Did not graduate from high school				–0.46 ± 0.17 <sup>b</sup>		
High-school graduation and higher				0		
Otological condition						1.8%
Present	–1.59 ± 0.46 <sup>a</sup>	–0.35 ± 0.16 <sup>a</sup>	–0.38 ± 0.17 <sup>a</sup>		–2.60 ± 0.78 <sup>b</sup>	
Absent	0	0	0		0	
BMI (kg/m <sup>2</sup> )						
≤20.5	–0.45 ± 0.53					
20.5–25	0					
>25	–1.52 ± 0.52 <sup>b</sup>					
Age at menarche (yr)						
<15.5				–0.44 ± 0.18 <sup>a</sup>		
15.5–17.5				–0.43 ± 0.16 <sup>b</sup>		
≥ 17.5				0		
Lifetime sexual experience						1.7%
Intercourse experience and living with a male partner			1.37 ± 0.30 <sup>b</sup>	0.14 ± 0.17	2.89 ± 1.38	
Intercourse experience			1.10 ± 1.19 <sup>b</sup>	0.50 ± 0.17 <sup>b</sup>	2.65 ± 0.86 <sup>b</sup>	
Kissing or dating experience			0.54 ± 0.19 <sup>b</sup>	0.43 ± 0.27	0.82 ± 0.87 <sup>a</sup>	
No experience			0	0	0	
GHQ-12 score ≥ 3						16.6%
No	4.93 ± 0.47 <sup>b</sup>	1.52 ± 0.16 <sup>b</sup>	0.70 ± 0.17 <sup>b</sup>	1.14 ± 0.15 <sup>b</sup>	8.15 ± 0.80 <sup>b</sup>	
Yes	0	0	0	0	0	

Predictors of SEI scores were categorized. Results are expressed as absolute scores relative to a reference category set to zero. Results correspond to final multiple regression models explaining each score (in columns); for instance, the mean general score being 17.5 score points for the entire group (Table 1), those with otological conditions have a mean score that is 1.59 points lower than those without, after adjustment on covariates.

Only variables with *P* values below 5% are shown: <sup>a</sup> *P* < 0.05; <sup>b</sup> *P* < 0.01.

(HR) 0.68 (95% confidence interval [CI] 0.50–0.93), and cardiac involvement [HR 0.57 (95% CI 0.39–0.83)] were associated with age at first kiss or date. Age at first kiss or date was not associated with paternal socioeconomic class, dysmorphic features, adult height, or BMI.

In univariate analysis, age at first intercourse was associated with age at onset of puberty and paternal socioeconomic class. In the final multivariate Cox model, lower paternal socioeconomic class [manual worker *vs.* nonmanual, HR 0.61 (95% CI 0.40–0.93)] and later age at onset of puberty [HR for a 1-yr delay in the onset of puberty: 0.90 (95% CI 0.83–0.96)] were associated with a lower proportion of women having experience of sexual intercourse. Age at first intercourse was similarly associated with age at menarche but was not associated with heart involvement, type of puberty, dysmorphic features, adult height, or BMI.

### Discussion

This is the first study to investigate the factors influencing self-esteem, social adjustment, and sexuality in a population-based cohort of women with Turner syndrome. Its results indicate that, in young women with Turner syndrome: 1) otological involvement and limited sexual experience are associated with lower self-esteem; 2) lower paternal socioeconomic class and an absence of sexual experience are associated with poorer social adjustment; 3) age at first kiss or date is related to the spontaneous occurrence of puberty and

the presence of cardiac abnormalities; and 4) age at first sexual intercourse is related to age at puberty and paternal socioeconomic class. Our study has implications for the management of patients with Turner syndrome, pubertal disorders, and, more generally, chronic illnesses of childhood.

Self-esteem was found to be low in several clinic- or support group-based samples of patients with Turner syndrome (31, 32). However, these studies were not population based, included patients from a wide range of age groups without taking age into account, and did not analyze factors associated with self-esteem and those related to pediatric care in particular. Ross *et al.* (32) suggested that the initiation of estrogen therapy was directly associated with an increase in self-esteem in 16-yr-old adolescents with Turner syndrome. Participants in our study were a mean of 6 yr older than the patients in Ross's study. This may account for our finding no effect of age at the onset of puberty on self-esteem. We demonstrated that otological involvement was a major, unrecognized factor affecting self-esteem, suggesting that ear infections during childhood should be aggressively managed. The other main factor associated with self-esteem was sexual experience, which increased self-esteem. Overweight was associated with lower self-esteem as also reported in the non-Turner population (33). The strong association between GHQ-12 scores and self-esteem illustrate the fact that psychological distress and self-esteem are strongly interrelated. Inclusion of GHQ-12 scores in the explanatory models of self-esteem determinants allowed us to adjust for the level of

**TABLE 3.** Determinants of social adjustment

Dimension	Social adjustment (lower scores indicate higher social adjustment)					% Variance of the overall score explained
	Family	Social, leisure	Work	Economic	Overall	
Range of values $r^2$	[1–5] <b>0.18</b>	[1–5] <b>0.22</b>	[1–5] <b>0.16</b>	[1–5] <b>0.07</b>	[1–5] <b>0.29</b>	
Age (yr)						
<20	0.26 ± 0.07 <sup>b</sup>					
20–22.5	0.17 ± 0.06 <sup>b</sup>					
22.5–25	0.12 ± 0.06					
≥25	0					
Paternal socioeconomic class						3.1%
Retired - inactive		0.16 ± 0.05 <sup>b</sup>	0.15 ± 0.05 <sup>b</sup>		0.14 ± 0.04 <sup>b</sup>	
Manual worker		0.18 ± 0.05 <sup>b</sup>	0.24 ± 0.05 <sup>b</sup>		0.14 ± 0.04 <sup>b</sup>	
Nonmanual worker		0	0		0	
Participant's educational level						
Age <20 yr			–0.07 ± 0.06			
Did not graduate from high school			–0.13 ± 0.05 <sup>a</sup>			
High-school graduation and higher			0			
Professional situation						2.2%
Professional activity		0.09 ± 0.05		0.04 ± 0.07	–0.03 ± 0.04	
Unemployed		0.21 ± 0.06 <sup>b</sup>		0.23 ± 0.08 <sup>b</sup>	0.14 ± 0.04 <sup>b</sup>	
Student		0		0	0	
Otological condition						0.7%
Present					0.08 ± 0.04 <sup>a</sup>	
Absent					0	
Lifetime sexual experience						5.9%
Intercourse experience and living with a male partner		–0.24 ± 0.09 <sup>b</sup>			–0.22 ± 0.06 <sup>b</sup>	
Intercourse experience		–0.41 ± 0.05 <sup>b</sup>			–0.22 ± 0.04 <sup>b</sup>	
Kissing or dating experience		–0.28 ± 0.05 <sup>b</sup>			–0.18 ± 0.04 <sup>b</sup>	
No experience		0			0	
Sexual experience at 20 yr						
Not evaluable			0.01 ± 0.08			
No			–0.15 ± 0.05 <sup>b</sup>			
Yes			0			
GHQ-12 score ≥ 3						17.3%
No	–0.48 ± 0.05 <sup>b</sup>	–0.35 ± 0.05 <sup>b</sup>	–0.39 ± 0.04 <sup>b</sup>	–0.41 ± 0.07 <sup>b</sup>	–0.39 ± 0.04 <sup>b</sup>	
Yes	0	0	0	0	0	

Predictors of SAS-SR scores were categorized. Results are expressed as absolute scores relative to a reference category set to zero. Results correspond to final multiple regression models explaining each score (in *columns*).

Only variables with *P* values below 5% are shown: <sup>a</sup>*P* < 0.05; <sup>b</sup>*P* < 0.01.

psychological distress and decrease the risk of false-positive relationship in the multivariate analysis.

Previous clinic-based studies based on small samples have reported that Turner syndrome patients have a limited social life, with satisfactory adjustment to this situation. A high proportion of older individuals with Turner syndrome are reported to hold university degrees and be employed below their academic level (2, 3). We found that sexual experience affected social adjustment, but, in contrast to what was observed for self-esteem, kissing or dating experience had an all-or-nothing effect. Sexual experience before the age of 20 yr was negatively associated with social adjustment at work, even after adjustment for educational level. Similarly to self-esteem, inclusion of the GHQ-12 score in the models allowed to adjust for the level of psychological distress.

Our findings concerning the effect of sexual experience on psychosocial adaptation led us to investigate the factors associated with the initiation of sexual activity. Individuals with Turner syndrome are known to have their first sexual experience later, to be less likely to establish a steady relationship with a partner, and to be less sexually active than women from the general population (reviewed in Ref. 31).

One study, including 80 women with Turner syndrome and a mean age of 34 yr, reported that 55% of these women had experience of sexual intercourse, with a mean age at first intercourse of 23 yr (34). In our study, 30% of the participants had had sexual intercourse by the age of 20 yr *vs.* 85% of women of the general population in France at the same age (26). Cardiac involvement was associated with dating beginning later, as would be expected given the severe adolescent morbidity associated with cardiac involvement. Age at the onset of puberty and type of puberty (spontaneous *vs.* induced), two closely related variables (9), were associated with age at first kiss or date. Differences were primarily associated with sustained spontaneous ovarian activity and persisted well after the age of 18 yr, when all participants had been exposed to estrogens. Androgen levels are reportedly low in adult women with Turner syndrome (35), and androgens play a role in female libido (36). It would therefore be of interest to evaluate the possible effects of androgen substitution on the initiation of sexual activity and psychosocial components in adolescents with Turner syndrome.

Daughters of manual workers tended to be older than daughters of non-manual workers at the time of first sexual

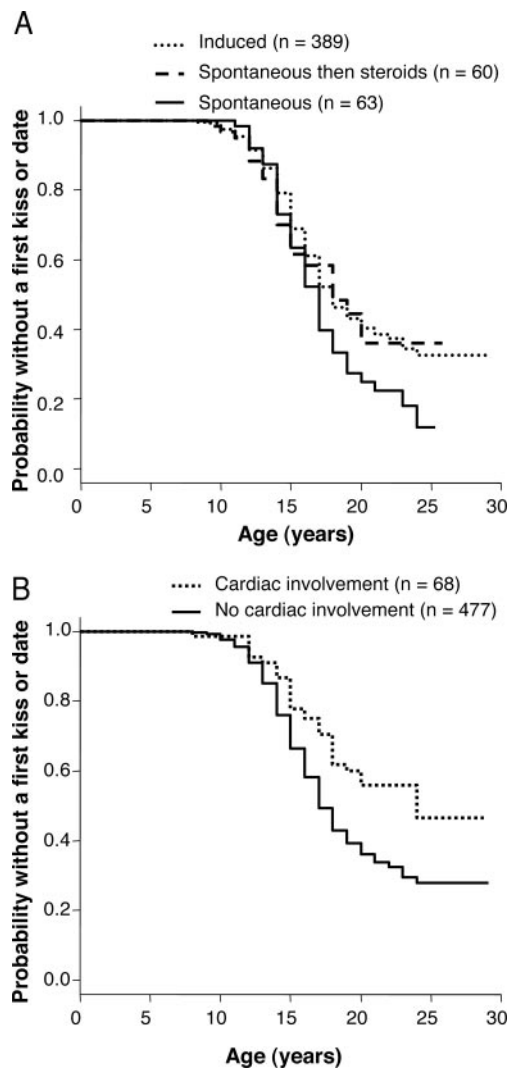


FIG. 2. Age at first kiss or date in women with Turner syndrome. The rate of event-free survival (the proportion of women with no experience of a first kiss or date) is shown and subdivided according to predictors significantly associated with events in the final multivariate Cox model (see text). A, Kaplan-Meier survival curves according to the type of puberty. B, Kaplan-Meier survival curves according to the presence of cardiac involvement.

intercourse, whereas in the general population, women from families with a low socioeconomic status tend to have sexual intercourse earlier (16, 17, 37, 38). This suggests that in patients from families with a higher socioeconomic status, the influence of Turner syndrome on relationships with the opposite sex is somewhat limited by coping strategies. Therefore, psychological counseling should particularly focus on women from lower socioeconomic status families. Age at puberty affected age at first sexual intercourse, and this effect persisted at least until the age of 25 yr when pubertal development had been underway for at least 7 yr in all girls. It is not possible to distinguish between psychosocial (*i.e.* having an age-appropriate physical development and therefore a better interaction with peers) and biological effects (*i.e.* a direct effect of sex steroids on the brain) based on our data. Nevertheless, our findings suggest that there may be a time

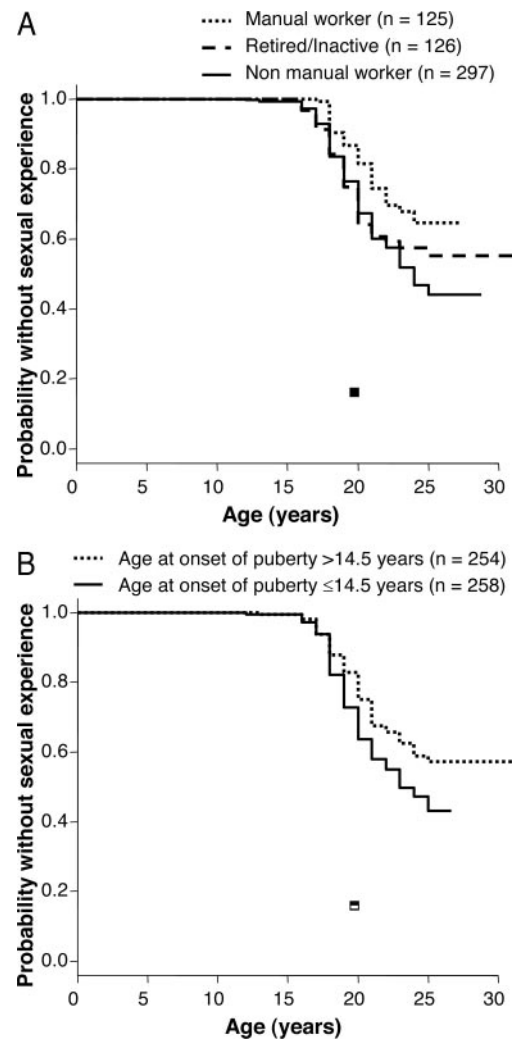


FIG. 3. Age at first sexual intercourse in women with Turner syndrome. The rate of event-free survival (the proportion of women who have not yet had sexual intercourse) is shown and subdivided according to predictors significantly associated with events in the final multivariate Cox model (see text). ■, Proportion of women without experience of sexual intercourse at the age of 20 yr in the general population in France (26). A, Kaplan-Meier survival curves according to paternal socioeconomic class. B, Kaplan-Meier survival curves for participants subdivided (upper or lower half of the distribution) according to age at initiation of puberty, defined as appearance of B2 stage or initiation of estrogen treatment.

window during which sex steroids must act on the brain at puberty to facilitate sexual behavior (39). Indeed, most studies in animal models (for male animals in most cases) have suggested that there is such a time window and that the consequences for sexual behavior of a lack of gonadal hormones during adolescence are irreversible (40).

Height and dysmorphic features were not associated with self-esteem and social adjustment, consistent with our results on health-related quality of life and calling into question the value of GH treatment (8). Furthermore, the lack of effect of height and dysmorphic features on sexual experience should help patients and health care providers to fight existing prejudices.

Several methodological aspects merit consideration. First,

there may be differences regarding the studied outcomes between the patients who did not participate in the study (31%) and those who did. Nevertheless, we obtained a response rate of 69%, which is within acceptable standards for an unsolicited nominative questionnaire. Second, self-esteem and social adjustment measures might have been too crude to evidence small differences. However, the validity and reliability of the SAS-SR and SEI questionnaires have been well established (23, 24), and these instruments have largely been used in nonpatient populations and in diverse psychiatric samples (41, 42) in both English and French (43, 44). Third, our study included only young adult patients with Turner syndrome who were living in France and had been treated with GH. Some conclusions may thus not be applicable to non-GH-treated patients or in different cultural contexts. Last, some of the observations regarding the influence of sexual life on psychosocial adjustment are probably not specific to Turner syndrome and should be evaluated in other patient and nonpatient groups.

The validity of Turner syndrome as a model for studying the influence of the timing of puberty on the initiation of sexual activity and its psychosocial consequences could be questioned. However, our findings call into question several practices in which pubertal timing is manipulated, generally as a means of controlling height. High-dose estrogen treatment is used to reduce height and GnRH agonists are used to increase it (19, 20, 22). Our data suggest that the long-term consequences of these interventions may extend well beyond the intended effect, calling into question the value of their continued use.

We conclude that puberty should be induced at a physiologically appropriate age in patients with Turner syndrome to optimize self-esteem, social adjustment, and the initiation of sexual activity. Psychological support and counseling should be offered to patients, focusing particularly on those from families with a low socioeconomic status. Our findings show that the long-term analysis of carefully followed cohorts of patients with chronic childhood diseases can bring to light unexpected observations that might improve pediatric care. They also call into question the use of drugs affecting the timing of puberty in patients with spontaneous puberty that would otherwise occur at a normal age.

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### References

- Ranke MB, Saenger P 2001 Turner's syndrome. *Lancet* 358:309–314
- Sybert VP, McCauley E 2004 Turner's syndrome. *N Engl J Med* 351:1227–1238
- Elsheikh M, Dunger DB, Conway GS, Wass JA 2002 Turner's syndrome in adulthood. *Endocr Rev* 23:120–140
- 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 2001 Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab* 86:3061–3069
- Stephure DK 2005 Impact of growth hormone supplementation on adult height in Turner syndrome: results of the Canadian randomized controlled trial. *J Clin Endocrinol Metab* 90:3360–3366
- van Pareden YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, Otten BJ, Hoorweg-Nijman JJ, Vulsma T, Stokvis-Brantsma WH, Rouwe CW, Reuser HM, Gerver WJ, Gosen JJ, Rongen-Westerlaken C, Drop SL 2003 Final height in girls with Turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab* 88:1119–1125
- Quigley CA, Crowe BJ, Anglin DG, Chipman JJ 2002 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* 87:2033–2041
- Carel JC 2005 Growth hormone in Turner syndrome: twenty years after, what can we tell our patients? *J Clin Endocrinol Metab* 90:3793–3794
- Soriano-Guillen L, Coste J, Ecosse E, Leger J, Tauber M, Cabrol S, Nicolino M, Brauner R, Chaussain JL, Carel JC 2005 Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. *J Clin Endocrinol Metab* 90:5197–5204
- Chernausk SD, Attie KM, Cara JF, Rosenfeld RG, Frane J 2000 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* 85:2439–2445
- Carel JC, Ecosse E, Bastie-Sigeac I, Cabrol S, Tauber M, Leger J, Nicolino M, Brauner R, Chaussain JL, Coste J 2005 Quality of life determinants in young women with Turner's syndrome after growth hormone treatment: results of the StaTur population-based cohort study. *J Clin Endocrinol Metab* 90:1992–1997
- Siegel PT, Clopper R, Stabler B 1998 The psychological consequences of Turner syndrome and review of the National Cooperative Growth Study psychological substudy. *Pediatrics* 102:488–491
- Lagrou K, Xhrouet-Heinrichs D, Heinrichs C, Craen M, Chanoine JP, Malvaux P, Bourguignon JP 1998 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* 83:1494–1501
- Downey J, Ehrhardt AA, Morishima A, Bell JJ, Gruen R 1987 Gender role development in two clinical syndromes: Turner syndrome versus constitutional short stature. *J Am Acad Child Adolesc Psychiatry* 26:566–573
- Downey J, Ehrhardt AA, Gruen R, Bell JJ, Morishima A 1989 Psychopathology and social functioning in women with Turner syndrome. *J Nerv Ment Dis* 177:191–201
- Goodson P, Evans A, Edmundson E 1997 Female adolescents and onset of sexual intercourse: a theory-based review of research from 1984 to 1994. *J Adolesc Health* 21:147–156
- Lam TH, Shi HJ, Ho LM, Stewart SM, Fan S 2002 Timing of pubertal maturation and heterosexual behavior among Hong Kong Chinese adolescents. *Arch Sex Behav* 31:359–366
- Kaltiala-Heino R, Kosunen E, Rimpela M 2003 Pubertal timing, sexual behaviour and self-reported depression in middle adolescence. *J Adolesc* 26:531–545
- Drop SL, De Waal WJ, De Muinck Keizer-Schrama SM 1998 Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 19:540–558

20. Yanovski JA, Rose SR, Municchi G, Pescovitz OH, Hill SC, Cassorla FG, Cutler Jr GB 2003 Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med* 348:908–917
21. Finkelstein JW, Susman EJ, Chinchilli VM, D'Arcangelo MR, Kunselman SJ, Schwab J, Demers LM, Liben LS, Kulin HE 1998 Effects of estrogen or testosterone on self-reported sexual responses and behaviors in hypogonadal adolescents. *J Clin Endocrinol Metab* 83:2281–2285
22. Carel JC, Ecosse E, Nicolino M, Tauber M, Leger J, Cabrol S, Bastié-Sigeac I, Chaussain JL, Coste J 2002 Adult height after long-term recombinant growth hormone treatment for idiopathic isolated growth hormone deficiency: observational follow-up study of the French population-based registry. *BMJ* 325:70–73
23. Coopersmith S 1981 SEI (Self-Esteem Inventories). Palo Alto, CA: Consulting Psychologists Press
24. Weissman MM, Bothwell S 1976 Assessment of social adjustment by patient self-report. *Arch Gen Psychiatry* 33:1111–1115
25. Goldberg D 1958 The detection of psychiatric illness by questionnaire. London: Oxford University Press
26. Spira A, Bajos N, Le groupe ACSF 1993 Les comportements sexuels en France. Paris: La Documentation Française
27. Rolland Cachera MF, Cole TJ, Sempé M, Tichet J, Rossignol C, Charraud A 1991 Body mass index variations: centiles from birth to 87 years. *Eur J Clin Nutr* 45:13–21
28. Altman DG 1991 Practical statistics for medical research. London: Chapman, Hall
29. Kaplan EL, Meier P 1958 Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–481
30. Cox DR 1972 Regression models and life tables (with discussion). *J R Stat Soc B* 34:187–220
31. Boman UW, Moller A, Albertsson-Wikland K 1998 Psychological aspects of Turner syndrome. *J Psychosom Obstet Gynaecol* 19:1–18
32. Ross JL, McCauley E, Roeltgen D, Long L, Kushner H, Feuillan P, Cutler Jr GB 1996 Self-concept and behavior in adolescent girls with Turner syndrome: potential estrogen effects. *J Clin Endocrinol Metab* 81:926–931
33. Fallon EM, Tanofsky-Kraff M, Norman AC, McDuffie JR, Taylor ED, Cohen ML, Young-Hyman D, Keil M, Kolotkin RL, Yanovski JA 2005 Health-related quality of life in overweight and nonoverweight black and white adolescents. *J Pediatr* 147:443–450
34. Pavlidis K, McCauley E, Sybert VP 1995 Psychosocial and sexual functioning in women with Turner syndrome. *Clin Genet* 47:85–89
35. Gravholt CH, Svenstrup B, Bennett P, Sandahl Christiansen J 1999 Reduced androgen levels in adult Turner syndrome: influence of female sex steroids and growth hormone status. *Clin Endocrinol (Oxf)* 50:791–800
36. Miller KK 2001 Androgen deficiency in women. *J Clin Endocrinol Metab* 86:2395–2401
37. Mott FL, Fondell MM, Hu PN, Kowaleski-Jones L, Menaghan EG 1996 The determinants of first sex by age 14 in a high-risk adolescent population. *Fam Plann Perspect* 28:13–18
38. Lammers C, Ireland M, Resnick M, Blum R 2000 Influences on adolescents' decision to postpone onset of sexual intercourse: a survival analysis of virginity among youths aged 13 to 18 years. *J Adolesc Health* 26:42–48
39. Sisk CL, Foster DL 2004 The neural basis of puberty and adolescence. *Nat Neurosci* 7:1040–1047
40. Schulz KM, Richardson HN, Zehr JL, Osetek AJ, Menard TA, Sisk CL 2004 Gonadal hormones masculinize and defeminize reproductive behaviors during puberty in the male Syrian hamster. *Horm Behav* 45:242–249
41. Serretti A, Cavallini MC, Macciardi F, Namia C, Franchini L, Souery D, Lipp O, Bauwens F, Smeraldi E, Mendlewicz J 1999 Social adjustment and self-esteem in remitted patients with mood disorders. *Eur Psychiatry* 14:137–142
42. Calabrese JR, Hirschfeld RM, Frye MA, Reed ML 2004 Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a U.S. community-based sample. *J Clin Psychiatry* 65:1499–1504
43. Guillon MS, Crocq MA, Bailey PE 2003 The relationship between self-esteem and psychiatric disorders in adolescents. *Eur Psychiatry* 18:59–62
44. Achard S, Chignon JM, Poirier-Littre MF, Galinowski A, Pringuey D, Van Os J, Lemonnier F 1995 [Social adjustment and depression: value of the SAS-SR (Social Adjustment Scale Self-Report)]. *Encephale* 21:107–116
45. Coopersmith S 1984 Manuel de l'inventaire d'estime de soi de S. Coopersmith SEI. Paris: Les Editions du Centre de Psychologie Appliquée

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