

## Original Article

# Prediction of Pubertal Growth at Start of Estrogen Replacement Therapy in Turner Syndrome

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**Abstract.** In estrogen replacement therapy in Turner syndrome, there is no report which recommends the timing of the start of estrogen therapy in relation to height or adult height prediction. We have established a prediction model for pubertal growth (height difference from the start of estrogen therapy until adult height) at the start of estrogen replacement therapy. Twenty-seven Turner girls without spontaneous puberty were divided into two groups according to birth years; Group I consisted of 16 patients born from 1980–1989 and Group II consisted of 11 patients born before 1980. Using clinical characteristics from Group I, stepwise multiple regression analysis taking pubertal growth as an independent factor, and chronological age, bone age (TW2 RUS method standardized for Japanese children), height and height SDS as dependent factors revealed following formula ( $p < 0.001$ ,  $R^2 = 0.737$ ): (pubertal growth) =  $-1.01x$  (Chronological age at start of E)  $-0.326x$  (height at start of E)  $-1.779x$  (bone age at start of E)  $+90.997$ . Predicted adult height was obtained by adding predicted pubertal growth to height at the start of estrogen therapy. The mean absolute difference between real adult height (tallest height after height velocity less than 1 cm/yr) and predicted adult height was  $1.6 \pm 0.9$  cm (0.3–2.8 cm) in Group I. When this prediction model was applied to Group II, The mean absolute difference between real adult height and predicted adult height was  $1.0 \pm 0.7$  cm (0.1–2.0 cm). A prediction model for pubertal growth at start of estrogen therapy in Turner syndrome was obtained. Using this prediction model, the timing of the start of estrogen therapy can be decided in consideration of the patient's desired adult height.

**Key words:** Turner syndrome, estrogen therapy, GH therapy, pubertal growth, adult height

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### Introduction

Turner syndrome is characterized by short stature, hypogonadism and minor anomalies (1).

It has been reported that approximately one third of Turner girls develop spontaneous puberty and one fifth experience menarche (2, 3). However, pubertal development in Turner syndrome sometimes does not reach maturity completely and 80–90 percent of Turner girls receive estrogen therapy during and/or after the adolescent period.

Saenger *et al.* (4) recommended that estrogen replacement therapy should be started before 15 yr of age, but should not be started before 12

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yr when adult height is taken into consideration. They also recommended that estrogen replacement should begin at one fourth to one sixth of the adult dose, and increase at 3 to 6 mo interval, to achieve full pubertal maturation in 2 to 3 yr, mimicing the slow natural pubertal development. Recently, Bondy (5) more strongly recommended starting low dose estrogen as early as 12 yr of age. However, there is no recommendation of timing of the start of estrogen therapy in relation to height or adult height prediction.

Pediatric endocrinologists of the Turner syndrome Research Collaboration (TRC) in Japan in answer to a questionnaire regarding the timing of the start of estrogen therapy, responded that chronological age is the most reliable factor, bone age the second, and height comes the third. Their ideal timing for the start of estrogen replacement was 12 yr to 14 yr of chronological age, 12 yr of bone age and 140 to 145 cm of height.

In this study, we analyzed the relation between timing of the start of estrogen therapy and height gain until adult height in Turner girls and propose recommending the timing of the start of estrogen therapy in consideration of adult height.

### Subjects and Methods

Among fifty-seven Turner girls who were born between 1971 and 1989 and had visited the Division of Endocrinology and Metabolism, National Children's Hospital/National Center for Child Health and Development, the patients who passed the following inclusion criteria were investigated: 1) no spontaneous puberty throughout the whole observation period; 2) received GH and estrogen therapy; and 3) reached their adult height. Adult height is defined as tallest height after height velocity less than 1 cm/yr. Twenty-seven patients who passed the inclusion criteria were divided into two groups according to their birth years: Group I consisted

of 16 patients born between 1980 and 1989, and Group II consisted of 11 patients born before 1980. The clinical characteristics of GH therapy in Groups I and II are shown in Table 1. Ages at the start and stop of GH therapy were significantly younger in Group I than in Group II, but height or height SDS at the start and stop of GH therapy was not significantly different between the two groups. The duration of GH therapy did not significantly differ between the groups.

In Group I, 13 patients received anabolic steroid (stanazolol). Their mean age and height at the start of anabolic steroid treatment were 12.1 yr and 128.8 cm ( $-2.82$  SD for Japanese female standard 1990), respectively. For eight of them, anabolic steroid was stopped before estrogen therapy and the remaining five had combined use of anabolic steroid and estrogen. All patients started estrogen therapy with conjugated equine estrogens (premalin) at various doses: 1 tablet (0.625 mg) in two patients, 1/2 tablet in three patients, 1/3 tablet in four patients, 1/4 tablet in four patients and 1/10, 1/5 and 2/5 tablets respectively for the remaining three patients. Growth hormone was started at 0.5 U/kg/wk (0.167 mg/kg/wk) for 12 patients and 1.0 U/kg/wk (0.33 mg/kg/wk) for four patients. In Group II, estrogen therapy was started at 1 tablet with or without medroxyprogesterone (provera).

Using the data from Group I, the Pearson's correlation coefficient between pubertal growth (height difference from the start of estrogen therapy until adult height) and clinical characteristics (chronological age, bone age and height) at start of estrogen therapy were calculated. The formula to predict pubertal growth was derived using stepwise multiple regression analysis. The projected adult height is calculated by converting height SDS of Turner syndrome at the start of GH therapy to adult height data of Turner syndrome without any treatment (6).

Bone age was estimated by one trained

**Table 1** Clinical characteristics of GH therapy in Groups I and II

	Group I	Group II	Significance
Number	16	11	
At start of GH therapy			
Age (yr)	9.42 ± 3.18	12.15 ± 2.10	p<0.05
Height (cm)	114.2 ± 15.0	124.6 ± 9.3	NS
Height SDS (SD)	-3.43 ± 1.01	-3.98 ± 0.96	NS
At stop of GH therapy			
Age (yr)	16.46 ± 1.68	19.09 ± 1.65	p<0.001
Height (cm)	147.3 ± 4.9	146.5 ± 4.3	NS
Height SDS (SD)	-1.95 ± 0.96	-2.27 ± 0.85	NS
Duration of GH therapy (yr)	7.04 ± 3.10	6.94 ± 2.83	NS
At start of estrogen therapy			
Age (yr)	15.38 ± 1.68	18.23 ± 1.60	P<0.0005
Height (cm)	144.2 ± 3.8	145.3 ± 3.4	NS
Height SDS (SD)	-2.34 ± 0.78	-2.48 ± 0.69	NS
Bone age (yr)	13.05 ± 0.76	12.94 ± 0.60	NS
At start of HRT			
Age (yr)	16.90 ± 1.71	18.93 ± 1.46	p<0.05
Height (cm)	147.9 ± 3.9	146.5 ± 4.0	NS
Height SDS (SD)	-1.89 ± 0.86	-2.29 ± 0.80	NS

doctor using the TW2 RUS method standardized for Japanese children.

The prediction formula obtained for Group I was then applied to Group II.

## Results

Table 1 shows the clinical characteristics of estrogen replacement therapy and cyclic estrogen-progesterone therapy (HRT). Ages at the start of estrogen therapy and HRT were significantly younger in the patients of Group I than in the patients of Group II. However height and height SDS at the start of estrogen therapy and HRT were not significantly different between the two groups. Table 2 shows pubertal growth, projected adult height (PAH), and clinical characteristics at adult height of the two groups. Pubertal growth was significantly greater in Group I than in Group II, while projected adult height, adult height and the effect of therapy were not significantly different. The difference

of adult height minus projected adult height, which is considered as the effect of the growth promoting therapy including GH, anabolic steroid and estrogen did not differ, either. Table 3 shows the correlation co-efficient between pubertal growth and clinical characteristics at the start of estrogen (E) therapy. Chronological age had the most strong negative correlation with pubertal growth.

Using stepwise multiple regression analysis taking pubertal growth as an independent factor, and chronological age, bone age, and height as dependent factors, we determined the following formula (p<0.001, R<sup>2</sup>=0.737):

$$(\text{pubertal growth}) = -1.01 \times (\text{Chronological age at start of E}) - 0.326 \times (\text{height at start of E}) - 1.779 \times (\text{bone age at start of E}) + 90.997$$

Although height did not correlate with pubertal growth by itself, stepwise multiple regression analysis showed it was a significant factor. Since bone age was missing for one patient

**Table 2** Pubertal growth, projected adult height, clinical characteristics at adult height and the effect of therapy

	Group I	Group II	Significance
Number	16	11	
Pubertal growth (cm)	5.1 ± 3.6	2.4 ± 2.0	p<0.05
Projected adult height at start of GH (cm)	140.8 ± 5.0	138.0 ± 4.8	NS
At Adult height			
Age (yr)	19.04 ± 2.12	20.71 ± 1.30	p<0.05
Height (cm)	149.3 ± 4.1	147.7 ± 4.2	NS
Height SDS (SD)	-1.71 ± 0.81	-2.04 ± 0.84	NS
Adult height-Projected adult height (cm)	8.6 ± 4.0	9.7 ± 4.4	NS

**Table 3** Correlation between pubertal growth and clinical characteristics at start of estrogen therapy

	correlation coefficient	significance
Chronological age	r = -0.699	p<0.005
Bone age	r = -0.663	p<0.01
Height	r = -0.396	p = 0.131
Height SDS	r = 0.124	p = 0.653

in Group I, the formula above was drawn from data of 15 patients in Group I. Predicted adult height is calculated as follows:

$$\begin{aligned} \text{(Predicted adult height)} &= \text{(Height at start of E)} \\ &+ \text{(Predicted pubertal growth)} = -1.01 \times \\ &\text{(Chronological age at start of E)} + 0.674 \times \\ &\text{(height at start of E)} - 1.779 \times \text{(bone age at} \\ &\text{start of E)} + 90.997 \end{aligned}$$

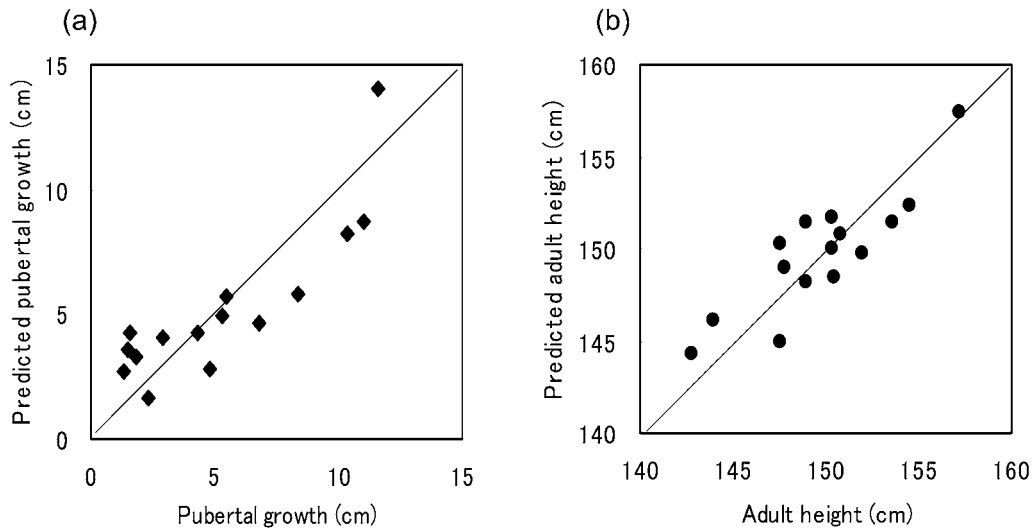
Figures 1 (a) and (b) show the correlation between real pubertal height and predicted pubertal height and between real adult height and predicted adult height in Group I. The mean absolute difference between real adult height and predicted adult height was 1.6 ± 0.9 cm (0.3–2.8 cm).

The formula for the prediction of adult height was applied to the patients in Group II. Since bone age was missing for two patients in Group II, the predicted pubertal growth and predicted adult height of nine patients in Group II were compared with real pubertal growth and real adult height (Fig. 2 (a) (b)). The mean absolute

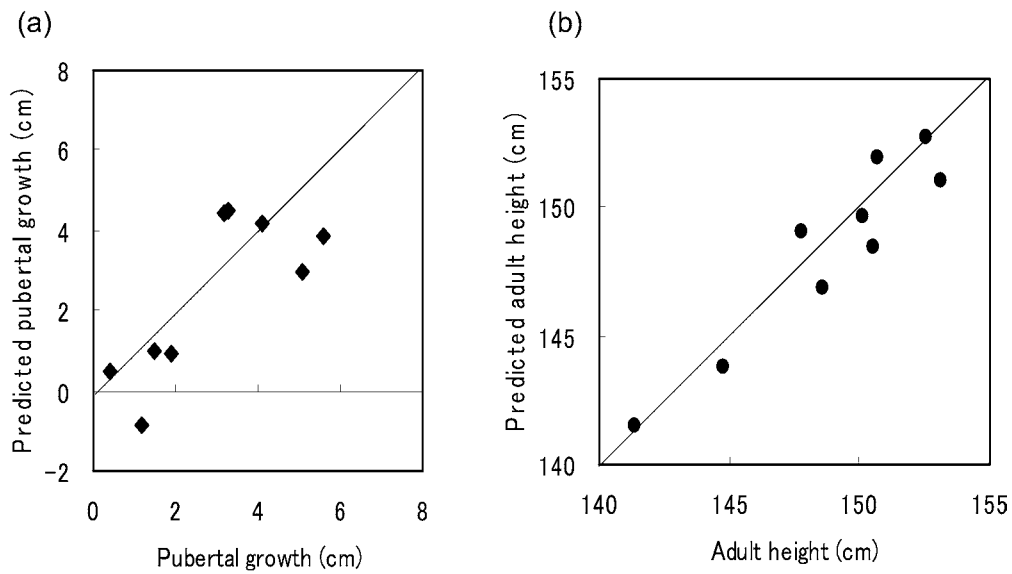
difference between real adult height and predicted adult height was 1.0 ± 0.7 cm (0.1–2.0 cm).

## Discussion

GH therapy was approved for Turner syndrome in 1991 in Japan, but approval was limited to Turner girls with GH deficiency (GHD) and the dose was low at 0.5 IU/kg/wk (0.167 mg/kg/wk). In 1999, the limitation of GHD was removed and the widely accepted dose for Turner syndrome, 1.0 IU/kg/wk (0.33 mg/kg/wk), was approved. The adult height of Turner syndrome was reported as 139.1 ± 5.6 cm without any treatment (6) and 142.4 ± 3.9 cm with anabolic steroid hormone treatment (7) in Japan. After innovation of GH therapy, the adult height of Turner syndrome was increased to 144.5 ± 5.2 cm at 0.5 IU/kg/wk and 147.0 cm at 1.0 IU/kg/wk of GH therapy (8). Although adult height of Turner girls was improved with GH therapy, GH is not as effective in Turner syndrome as in GHD. The mean growth velocity in the first year



**Fig. 1** Pubertal growth and predicted pubertal growth (a), and adult height and predicted adult height (b) in Group I.



**Fig. 2** Pubertal growth and predicted pubertal growth (a), and adult height and predicted adult height (b) in Group II.

of therapy is 8.5 cm/yr at 0.5 IU/kg/wk in GHD (9) and 6.3–7.2 cm/yr at 1.0 IU/kg/wk in Turner syndrome (10). The adult height of GHD girls has been reported as  $147.8 \pm 5.4$  cm (11), which is not so different from that of the Turner girls of Groups I and II.

In Turner syndrome, although response to GH therapy is poor, improved adult height is obtained by delaying estrogen replacement therapy. Because of hypogonadism, bone age decelerates at around 10.5 yr (12) and taller adult height can be obtained if estrogen replacement

**Table 4** Predicted adult height at 140 cm of height

Chronological age (yr)	Height (cm)	Height SDS (SD)	Bone age (yr)	Predicted pubertal growth (cm)	Predicted adult height (cm)
12	140	-1.41	11	13.7	153.7
13	140	-2.34	11.5	11.8	151.8
14	140	-3.00	12	9.9	149.9
15	140	-3.29	12.5	8.0	148.0

is started at an older age (13). In this study, the mean adult height was not significantly different between Groups I and II, although age at the start of GH therapy was older and height SD score was lower in Group II than in Group I. The same adult height was achieved by starting estrogen replacement therapy later, by approximately three years, in Group II than in Group I.

The most recent guideline on the management for Turner syndrome recommends inducing pubertal development at 12–13 yr of age to avoid psychological problems and reduced bone mineral density caused by delayed start of estrogen replacement therapy (5). However, patients' and their parents' desired adult height cannot be ignored in clinical practice. Puberty is the period in which sexual characteristics mature, during which growth velocity accelerates, decelerates and finally stops. It is necessary to predict adult height if a patient's desired adult height is to be taken into account. A formula to predict pubertal growth at the start of estrogen therapy was derived from age, height and bone age using stepwise multiple regression analysis. Adult height can be predicted by adding predicted pubertal growth to height at the start of estrogen therapy. Estrogen therapy in Group I was variable. Since the patient with the lowest dose (1/10 conjugated equine estrogens) had no bone age data, her data was not used to derive the prediction formula. Very low dose estrogen therapy is recommended and it may induce greater pubertal growth. Since there was no significant correlation between initial estrogen dose and pubertal growth (data not shown) in

Group II, it seems that pubertal growth is not influenced by an initial estrogen dose greater than 0.2 tablets of conjugated equine estrogens. The prediction model was applied to Group I and pubertal growth was predicted very well with a maximum difference of 2.0 cm. However, it should be noted that the prediction was established and tested in subjects with estrogen therapy initiated at considerably advanced ages.

Recently, it has been recommended that very low dose estrogen therapy such as transdermal estradiol 6.25  $\mu\text{g}$  daily or micronized estradiol 0.25 mg daily oral administration is started at a young age to mimic the process of normal puberty (5). In Japan, conjugated equine estrogens (premalin) 0.0625 mg daily oral administration, transdermal estradiol 0.09 mg every two days or estradiol 1 ng daily oral administration (14) have been used as very low dose estrogen therapy. Although we don't have enough data on very low dose estrogen therapy, the present prediction model may imply that the therapy will not shorten pubertal growth but rather increase pubertal growth.

In our experience, patient's or parents' desired adult height is at least 150 cm. Various situations were tested with this prediction model. In the case of a Turner girl of 140 cm height at 12 yr of age, pubertal growth is predicted as 14.3 cm and adult height is predicted as 154.3 cm, provided the prediction can be adequately extrapolated to an earlier start of estrogen therapy. As shown in Table 4, a height at 140 cm seems to be a critical point for starting estrogen therapy in consideration of adult height.

However, it is sometimes difficult to treat Turner girls of 140 cm until 14 yr of age, early diagnosis and early initiation of GH treatment is very important.

From the consensus statements and the present study, the following therapy can be recommended in consideration of favorable adult height for Turner girls during childhood: 1) start GH therapy at 0.35 mg/kg/wk as early as 8 yr with greater than  $-2.5$  SD of height SDS; 2) start very low dose estrogen therapy at 12–14 yr at approximately 140 cm of height; 3) dose of estrogen is gradually increased every 3–6 mo; 4) start cyclic estrogen-progesterone therapy approximately 2 yr after start of low dose estrogen therapy. Further studies related to early GH treatment, anabolic steroid treatment and low dose estrogen treatment are necessary.

In summary, a prediction model for pubertal growth at the start of estrogen therapy in Turner syndrome was derived. Using this prediction model, timing the start of estrogen therapy can be decided in consideration of the patient's desired adult height.

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