

Optimizing Estrogen Replacement Treatment in Turner Syndrome

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ABSTRACT. Estrogen has a biphasic effect on growth, stimulatory at low doses but inhibitory at higher doses. Therefore, designing optimal sex hormone replacement treatment in girls with Turner syndrome (TS) who are being treated with growth hormone (GH) involves considering the dose and form of the estrogen as well as the route and timing of its administration. We report here a preliminary analysis of a study to test the concept that an optimal estrogen replacement regimen should consist of estradiol administered in a low dose by a systemic route.

The study population consisted of 9 girls with TS who had been treated with GH for 6 or more months. When the girls were 12 to 15 years old, we added depot estradiol at a monthly intramuscular dose of 0.2 mg and increased the dose at 6-month intervals to 0.4, 0.6, and, in 7 of the girls, 0.8 mg. We compared the results in these subjects with those in a matched group of 37 patients with TS in whom routine estrogen treatment had been started at similar ages and who were treated with a similar course of GH therapy.

The gain in height at 2 years was 2.6 cm greater in those who were treated with depot estradiol than in those who were treated with routine estrogen. The bone age in the patients who were treated with depot estradiol increased in proportion to their chronologic age, suggesting that this difference indicates an increase in their predicted adult height. We conclude that using very low doses of systemic estradiol to induce puberty before the age of 15 years in girls with TS who are treated with GH, instead of using routine estrogen therapy, can result in increased final heights. *Pediatrics* 1998;102:486–488; *Turner syndrome, estrogen replacement, growth hormone, estradiol.*

ABBREVIATIONS. GH, growth hormone; TS, Turner syndrome.

The secretion of estrogen during puberty contributes to the growth spurt of early puberty,^{1,2} with evidence for both indirect effects, which are mediated by an increase in the secretion of growth hormone (GH),³ and direct effects on cartilage growth.⁴ However, pharmacologic estrogen treatment blunts growth,⁵ in part by attenuating the action of GH.⁶ Determining the estrogen replacement regimen that is optimal for use concurrently with GH therapy has become a practical issue in the management of Turner syndrome (TS), which is characterized by both short stature and gonadal dysgenesis.

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A number of factors must be considered in designing optimal sex hormone replacement therapy in TS. One is the timing of the estrogen administration. Might delaying estrogen give endogenous or exogenous GH more time to act? This issue was addressed recently by Attie and associates.⁷ Estrogen was added to GH therapy in girls with TS at either 12 or 15 years of age, and the patients were followed from 12 years of age until near adult height. Estrogen was given in the form of conjugated equine estrogens (Premarin); the dosage was 0.3 mg/d for the first 6 months and then 0.6 mg/d with medroxyprogesterone acetate 10 mg/d added for 1 week each month. The total growth from 12 years of age to near adult height averaged 13.0 cm in the group in whom estrogen was begun at 12 years and 15.8 cm in those in whom it was begun at 15 years; this difference was highly significant. These investigators concluded that delaying the initiation of estrogen therapy was advantageous to growth.

Another consideration in optimizing the therapy is the form of the estrogen. Estradiol is the natural form of estrogen that is secreted and binds to the estrogen receptor in humans.⁸ Ethinyl estradiol is an analogue of estradiol with an ethinyl group covalently attached at the 17 α position. Ethinyl estradiol is not metabolized to estradiol but is taken up in unmodified form and retained by estrogen target tissues for a longer time than is estradiol.⁹ The estradiol precursor estrone acts after being metabolized to estradiol.^{9,10} Equine estrogens, the major components of the widely used drug Premarin, are not estradiol precursors.

The route of estrogen administration also must be considered. Estradiol is normally secreted into the systemic circulation; thus, the liver receives the same dose as other somatic tissues. In contrast, estrogen given orally reaches the systemic circulation only after absorption into the portal venous system and after metabolism by the liver.¹¹ In this situation, the liver is exposed to a greater dose of estrogen than is the rest of the body; thus, hepatic protein production is affected disproportionately.¹² Orally administered estradiol is relatively ineffective systemically because it is extensively metabolized by the liver to estrone metabolites before it reaches the systemic circulation. Ethinyl estradiol, estrogen sulfates, and equine estrogens are effective orally because they are relatively protected from hepatic metabolism.

Finally, the estrogen dose must be considered. It is well known that estrogen has a biphasic effect on growth and that high doses inhibit growth and the generation of somatomedin-C.⁶ These effects of estrogen have been taken advantage of in treating acromegaly¹³ and excessive stature,⁵ because they antagonize the effects of GH at the target organ level.

On the other hand, low doses of estrogen stimulate linear growth in hypogonadal girls. Depot estradiol at a dose of 1 to 1.5 mg/mo stimulates growth during puberty.¹ Ethinyl estradiol at a dose of ~4 µg/d stimulates the growth rate; at higher doses it inhibits it.¹⁴

Physiologic considerations suggest that progestin is unnecessary early in the induction of puberty. Progesterone is not normally secreted by the ovary in substantial amounts until a corpus luteum has formed after ovulation has occurred. Furthermore, half of all menstrual cycles are anovulatory for the first 2 years after menarche. Therefore, progestin replacement appears not to be physiologic until after a few years of estrogen treatment.

With these considerations in mind, we concluded that an optimal hormone replacement regimen would be estradiol administered in low doses by a systemic route. We present here a preliminary analysis of data from a study of such a regimen in 9 patients with TS.

METHODS

We enrolled 9 otherwise healthy patients with TS in a multicenter study at 12 to 15 years of age, after they had been treated with GH for at least 6 months and had given informed consent. They were given depot estradiol in gradually increasing doses while their GH therapy was continued. The depot estradiol was given as a single monthly intramuscular injection. An injection of 1.5 mg of depot estradiol causes cyclic changes in the levels of estradiol in the blood; the levels peak at 4 to 7 days, and the drug is undetectable by 3 weeks.¹⁵ We used smaller doses of depot estradiol than have been reported previously;¹ our regimen approximates the normal tempo of puberty (unpublished data). The starting dose was 0.2 mg/mo, and the dose was increased at 6-month intervals to 0.4, 0.6, and 0.8 mg/mo. Two of the patients dropped out of the study after 18 months of treatment; thus, only 7 patients were left at the end of the 2-year study. In addition to height and growth rate, we evaluated bone age and Bayley-Pinneau predicted height,¹⁶ as well as pubertal milestones.

We compared the growth in these patients with that in girls with TS in the National Cooperative Growth Study database who were treated with routine estrogen therapy. From 152 patients in the database in whom estrogen had been started at 12 to 15 years of age and who also had been treated with GH for at least 6 months, we matched a subgroup of 37 on the age at which the estrogen was started and on the duration of GH treatment before estrogen. Routine estrogen treatment in the 11 patients in the database taking equine estrogens was ≤0.15 mg every other day in 2 patients, 0.3 mg every other day in 4 patients, and ≥0.3 mg daily in 5 patients.

RESULTS

The mean age at the initiation of estrogen therapy was 12.9 years in both groups. The mean duration of GH therapy before estrogen therapy was 2.9 years in the patients who were treated with depot estradiol and 3.0 years in those who were treated with routine estrogen. The growth rate increased during the first 6 months of treatment in 7 of the 9 patients who were given depot estradiol. In 4 of these 7, it remained above the pretreatment rate at 1 year. On average, the growth rate increased slightly during the first 6 months, was very close to baseline at 1 year, and then gradually decreased to below the baseline rate. The mean height of the girls who were treated with depot estradiol increased by 9.0 cm at 18 months and by 12.7 cm at 2 years.

The growth rate in the girls who were treated with

routine estrogen decreased significantly at each 6-month interval. Their mean height increased by 7.6 cm at 18 months and by 10.1 cm at 2 years. The difference in height gained over the treatment period was significant, with the girls who were treated with depot estradiol having gained 1.4 cm more at 18 months than those who were treated with routine estrogen and 2.6 cm more at 2 years ($P < .001$). Data on the growth rates in the two groups are presented in Table 1.

Additional analysis of the data on the girls who were treated with depot estradiol showed that, on average, their bone age increased by 1 year for every year of treatment. As a consequence, their mean height predicted by the Bailey-Pinneau method increased by 5.8 cm over the 2-year treatment period. The entire increase took place in the first year after treatment was begun. The height predicted after 2 years of depot estradiol therapy was not correlated with the age at which the therapy was started.

DISCUSSION

The growth rate in patients with TS who are treated with GH can be expected to wane during continued therapy,¹⁷ but in 7 of our 9 patients who were treated concurrently with depot estradiol, the growth rate actually increased in the first 6 months. Furthermore, in 4 of the 9, it remained at or above baseline after the first year. With depot estradiol, their bone age increased at a normal rate, and, consequently, their height predicted by the Bayley-Pinneau method increased substantially, with this increase occurring during the first year of treatment. The lack of correlation of age at initiation of therapy with height potential at the end of 2 years of therapy with depot estradiol suggests that very low dose systemic estradiol possibly can be initiated at 12 years of age without any loss of height potential. In contrast, initiating routine estrogen therapy at 12 years of age is associated with a loss of height potential.⁷ Therapy with depot estradiol led to an average of 2.6 cm more growth over a 2-year period than did routine estrogen therapy, a highly significant difference both statistically and in practical terms. This difference is equivalent to that gained in about 1 year of GH therapy: during 6 years of GH therapy, the mean height of patients with TS increased by 12 cm more than expected, with most of this gain coming in the early years of GH therapy.¹⁷

TABLE 1. Growth Rates in TS With Concurrent GH and Depot Estradiol or Routine Estrogen Treatment

Month	Growth Rate (cm/y)				
	GH		GH + Estrogen		
	0	6	12	18	24
Depot estradiol	5.7 ± 0.9	6.9 ± 0.8	6.2 ± 0.8	5.0 ± 0.8	3.8 ± 0.7*
Routine estrogen	6.0 ± 0.2	5.6 ± 0.2*	5.1 ± 0.2*	4.6 ± 0.2*	4.0 ± 0.1*

Values are mean ± SEM. $n = 9$ through month 18, 7 thereafter (depot estradiol); 37 through month 18, 28 thereafter (routine estrogen).

* $P < .05$ vs month 0.

The importance of this study is that it suggests that the final height of patients with TS who are treated with GH is increased by using very low doses of systemic estradiol, rather than routine estrogen therapy, to induce puberty. The gain seems equivalent to that achieved with 1 year of GH therapy alone. A trial with a larger number of patients will be required to confirm these data and to determine the long-term consequence of this intervention strategy on bone mineralization.

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The Psychological Consequences of Turner Syndrome and Review of the National Cooperative Growth Study Psychological Substudy

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ABSTRACT. *Objective.* To present longitudinal data on the psychological profile of a cohort of girls with and without Turner syndrome (TS) treated for 3 years with growth hormone (GH).

Methods. Among a sample of 283 children with short stature, 37 girls with TS were recruited at 27 US medical centers. Of the original cohort, 22 girls with TS, 13 girls with isolated growth hormone deficiency (GHD), and 12 girls with idiopathic short stature were followed through 3 years

of GH therapy. All were school-age, were below the 3rd percentile for height, had low growth rates, and were naive to GH therapy. Psychological tests (the Wide Range Achievement Test and the Slosson Intelligence Test) were administered to the clinical groups within 24 hours of their first GH injection and yearly thereafter. Control subjects were 25 girls with normal stature matched for age and socioeconomic status, who were tested only at baseline. One parent of each subject also completed the Child Behavior Checklist for that subject.

Results. At baseline, the clinical groups had more internalizing behavioral problems, had fewer friends, and participated in fewer activities than did the control subjects. The groups did not differ in mean IQ or academic achievement, but the TS group did have more problems in mathematics achievement. Height and growth rate significantly increased in the clinical groups over the 3 years of GH therapy, but IQ and achievement scores did not. Significant linear reductions were noted in both Internalizing and Externalizing Behavior Problems after GH treatment, with the TS group having fewer behavior problems before and after GH treatment than did the GHD-idiopathic short

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