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ORIGINAL ARTICLE

Effects of growth reduction therapy using high-dose 17β-estradiol in 26 constitutionally tall girls

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Summary

Objective The efficacy and safety of height-limiting therapy with high-dose 17β-oestradiol in girls with constitutionally tall stature (CTS) are controversial. We evaluated the effectiveness of high-dose 17β-oestradiol in premenarchal girls with CTS treated until their bone age reached 14 years.

Design We retrospectively reviewed the medical records of the girls managed between 1989 and 2000 with high-dose 17β-estradiol for CTS with a predicted final height greater than +3SDs.

Patients Twenty-six girls met our inclusion criteria. At baseline, mean chronological age was 12·06 ± 1·51 years and mean height was 171·1 ± 6·5 cm with a height standard deviation score of 4·5 ± 0·24, and mean predicted final height was 183·0 ± 4·2 cm. Treatment was stopped when bone age reached 14 years; mean treatment duration was 1·62 ± 0·76 years.

Measurements The following were obtained at 6-month intervals: height, body weight, Tanner stage, bone age, plasma cholesterol and triglycerides, plasma glucose and side effects. A mailed questionnaire on final height and satisfaction was sent 2 years after treatment discontinuation (response rate, 24/26).

Results Final height was significantly ($P < 0·001$) reduced, by 2·4 ± 3·2 cm, as compared to predictions. High-dose 17β-estradiol therapy decreased growth velocity and significantly increased skeletal maturation ($P < 0·001$). Linear growth after treatment discontinuation was 3·3 ± 1·9 cm. No serious side effects were recorded. Most of the patients were satisfied with the treatment.

Conclusion High-dose 17β-estradiol was moderately effective in reducing final height and should probably be reserved for selected patients, particularly as knowledge on potential long-term side effects is lacking.

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Introduction

The use of sex steroids to reduce final height in patients with constitutionally tall stature (CTS) remains controversial. CTS is defined as an SD of at least 2 above the mean height for sex and chronological age in a relevant reference population,[1] after exclusion of overgrowth syndromes.[1–3] Although CTS is related primarily to familial factors, nutrition,[1,2] hormonal status and socioeconomic environment also exert major effects on growth.

The diagnosis usually rests on a family history of tall stature and on physical findings distinguishing CTS from overgrowth syndromes.[1–3] Evaluation of the tall girl should include a medical history, physical examination, estimation of growth potential and a battery of laboratory tests.[3]

Bone growth and maturation result from a complex interplay of multiple hormones and growth factors.[1,4] At puberty, sex steroids, predominantly oestrogens in girls (in combination with other hormones and growth factors), induce an increase in growth velocity followed by closure of the epiphyseal growth plates with cessation of linear growth in long bones.[4] High-dose oestrogens may accelerate growth plate closure without increasing growth velocity, thus reducing the final height compared to the predicted final height.[1,5] Selecting patients for high-dose oestrogen therapy depends on an accurate estimation of final height: treatment is usually considered only when the predicted final height exceeds 3 SDs above the mean in the general population.[6,7]

Thus, predicting final height plays a crucial role in the management of children with CTS.[6,8] The most widely used method for predicting final height, which was devised by Bailey and Pinneau (BP method), is well suited to clinical practice but is highly dependent on the ability to obtain an accurate estimation of bone age.[9–11] Height prediction using the BP method in children with CST has been found inaccurate in boys but clinically acceptable in girls.[6]

Numerous publications have confirmed the effectiveness of high-dose oestrogen therapy in slowing linear growth in girls.[1,3,6,12–15] Other studies found that high-dose oestrogens accelerated bone maturation.[7,12–14,16–19] To date, the main oestrogens used for growth inhibition have been conjugated oestrogens and ethinyl oestradiol.[12,20,21] Side effects of high-dose oestrogen therapy for growth inhibition have been reported, and the risk/benefit ratio remains unclear, most notably regarding the risk of cancer[22] and thromboembolism.[23–25] As compared to conjugated oestrogens or ethinyl oestradiol, 17β oestradiol has shown a better metabolic safety profile, with less weight gain, dyslipidaemia and thromboembolism.[26] In this

study, we therefore examined the height-limiting effect and tolerance of oral 17β estradiol in 26 constitutionally tall girls.

Subjects and methods

Between 1989 and 2000, 26 premenarchal constitutionally tall girls completed 17β-estradiol treatment at the Paediatric Endocrinology and Gynaecology Department of the Necker-Enfants Malades Teaching Hospital, Paris, France. CTS was defined as a height (expressed as the SD of observed height for age) equal to or greater than 2 SDs at referral, after exclusion of other causes of excessive growth. Treatment was offered to patients who requested height-limiting therapy and whose predicted height was at least 179 cm (+3 SD for the general population in France).[27] Consent of the parents was obtained. The girls were treated with 4·0–8·0 mg/day of 17β-estradiol, combined with the progestogen chlormadinone acetate, 10 mg/day and 15 days/month to induce cyclic bleeding and to avoid over-stimulation of the endometrium. The dose of 8 mg of 17β-estradiol was chosen in the majority of patients because of the following bioequivalence: 8 mg is equivalent to 0,10 mg of ethinyl oestradiol and because it has been found to be efficacious for height reduction in tall stature.[28] The treatment was stopped when bone age reached 14 years. This BA was chosen at the beginning of the study because it meant that that at least 98% of growth had been completed. Throughout treatment, patients were evaluated at 6-month intervals for measurement of body weight and height, Tanner stage determination and recording of side effects. All height measurements were performed using the same stadiometer. Radiographs of the left hand and wrist were also obtained at each evaluation for bone age assessment, which was performed by a single experienced physician using the Greulich and Pyle method.[10] Bone age acceleration was calculated based on the bone age increase from baseline to the 6- and 12-month time points. Final height was predicted using the tables of Bayley and Pinneau.[9] Final height reduction was computed as the difference between predicted height at baseline and observed final height (see succeeding discussions). Plasma levels of cholesterol, triglycerides ($n = 10$) and glucose were measured to monitor safety.

All patients were sent a questionnaire by mail at least 2 years after treatment discontinuation. The questionnaire items included height, which was therefore used as final height in the study, treatment acceptance, patient satisfaction with the treatment, body weight and regularity of menstrual cycles. Of the 26 patients, 24 returned completed the questionnaires.

Table 1. Baseline clinical features in 26 girls with constitutionally tall stature treated with high-dose 17β-oestradiol

Clinical features	Mean ± SD	Range
Chronological age (years)	12·06 ± 1·51	8·75–15·50
Height (cm)	171·1 ± 6·5	152·6–180·0
Height SD	4·55 ± 0·24	3·00–7·60
Bone age (years)	11·92 ± 0·96	10–13
Predicted final height (cm)	185·4 ± 4·3	176·6–195·3
Body mass index	18·62 ± 0·29	16·07–21·53

Data are means ± SD.

Statistics

Results are reported as mean (SD) values with the 95% confidence interval (95%CI) and standard error (SE). Student's *t*-tests were performed, and analysis of variance was used to evaluate the influence of variables on treatment effects. *P* value of $< 0·05$ were considered statistically significant.

Results

Clinical data (Tables 1 and 2)

At baseline, mean chronological age was 12·06 ± 1·51 years and mean height was 171·1 ± 6·5 cm with a height SDS of 4·5 ± 0·24. Mean treatment duration was 1·62 ± 0·76 years. Predicted final height was 185·4 ± 4·3 cm, height at treatment discontinuation was 179·7 ± 3·7 cm and final height was 183·0 ± 4·2 cm. The mean reduction in final height was 2·4 ± 3·2 cm, which was statistically significant ($P < 0·001$).

Throughout treatment, skeletal maturation was accelerated and growth rate was decreased. During the first 6 months of therapy, bone age increased by 1·0 ± 0·33 years, indicating a significant acceleration of bone age ($P < 0·001$) consistent with 17β-estradiol-induced stimulation of cartilage maturation. Bone age acceleration remained significant when the first year of treatment was considered (Table 3). After treatment discontinuation, height continued to increase, with the mean gain being 3·3 ± 1·9 cm. Thus, final height was significantly higher ($P < 0·001$) than height at treatment discontinuation. However, the final height predicted at treatment

Table 2. Height parameters during and after high-dose 17β-oestradiol therapy in 26 girls with constitutionally tall stature

Height parameters	Mean	SD	SE	95% confidence interval
Height at baseline (cm)	171·1	6·5	1·27	168·5–173·7
Predicted final height (cm)	185·4	4·3	0·84	183·7–187·2
Height at end of treatment (cm)	179·7	3·7	0·75	178·0–180·9
Predicted height at end of treatment	183·1	3·3	0·68	181·6–184·5
Final height (cm)	183·0	4·2	0·86	181·2–184·8
Reduction in final height (cm)	2·4	3·2	0·66	1·2–3·9
Post-treatment growth (cm)	3·3	1·9	0·38	2·5–4·1

Table 3. Bone age and growth rate during high-dose 17β-oestradiol therapy in 26 constitutionally tall girls

Treatment duration (months)	0–6	6–12
Bone age acceleration (years) (SD)*	1·05 ± 0·33 $P < 0·001$	0·6 ± 0·36 $P < 0·001$
Growth rate (cm)	3·56 ± 2·40	2·22 ± 1·38

*Bone age acceleration was calculated as the difference between baseline bone age and age after 6 and 12 months of therapy, divided by 6 and 12 months, respectively.

Table 4. Height parameters during and after high-dose 17β-oestradiol therapy in the three patient subsets based on the relationship between bone age and chronological age (overall population, $n = 26$)

	BA < CA ($n = 10$)		BA = CA ($n = 7$)		BA > CA ($n = 9$)	
Data	Mean	SE	Mean	SE	Mean	SE
Height at baseline (cm)	174·5	1·3	167·2	2·0	170·4	2·6
Predicted final height (cm)	186·2	0·9	182·1	1·5	187·2	1·6
Height at end of treatment (cm)	180·4	1·2	176·7	1·0	180·7	1·0
Predicted height at end of treatment	183·3	1·1	180·5	1·0	184·1	1·1
Final height (cm)	183·8	1·4	179·1	1·0	184·3	1·3
Reduction in final height (cm)	2·4	1·1	3·0	1·2	2·9	1·0
Post-treatment growth (cm)	3·4	0·8	2·4	0·7	3·6	0·4

discontinuation was not significantly different from the final height recorded at last follow-up.

To evaluate the effect of therapy according to bone maturation at baseline, we divided the patients into three groups based on whether bone age at baseline was less than chronological age (BA < CA, $n = 10$), equal to chronological age (BA = CA, $n = 7$) or greater than chronological age (BA > CA, $n = 9$) (Table 4). The BA < CA group had the highest values for mean baseline height (174·5 cm) and final height (183·8 cm); post-treatment growth was 3·4 cm and final height reduction was 2·4 cm. The BA = CA group had the lowest values for mean baseline height (167·2 cm), final height (179·1 cm), post-treatment growth (2·4 cm) and final height reduction was 3·0 cm. In the BA > CA group, mean baseline height was intermediate between the other two groups (170·4 cm). This group had the highest values for predicted final height (187·2 cm), final height (184·3 cm) and post-treatment growth (3·6 cm); final height reduction was 2·9 cm. By analysis of variance, none of these differences was statistically significant. Thus, the relationship between bone age and chronological age at baseline had no influence on treatment effects in our cohort of 26 patients.

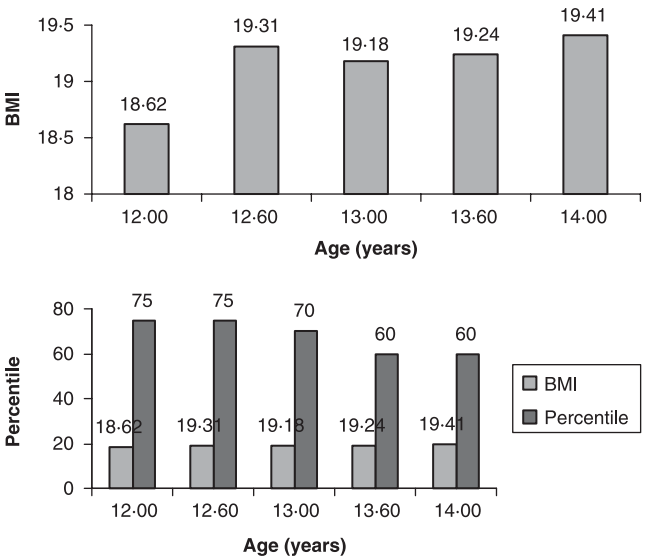

Fig. 1 Body mass index (BMI) variations during the first 2 years of 17β-oestradiol therapy in 26 girls with constitutionally tall stature (values in the upper panel and with percentile according to age in the lower panel).

Side effects of treatment

Overall tolerance was good in our group of patients. No serious side effects were noted. Five girls had one or more of the following: fatigue, nausea, breast discomfort, abdominal pain and triglyceride elevation. However, breast discomfort was reported by a single patient, suggesting that high-dose 17β-estradiol therapy may have little influence on breast development.

Glucose metabolism was normal in all patients. Of the 10 patients who underwent triglyceride assays, only one had triglyceride elevation during therapy with a return to normal after treatment discontinuation. No blood pressure changes were found, and no thromboembolic events were recorded. Body mass index during treatment did not vary significantly (Fig. 1). Spontaneous cyclical bleeding occurred in 24 patients within 6 months and in two patients within 11 months after treatment discontinuation. These data suggest that side effects were mild during treatment, although the small sample size and short follow-up should be borne in mind. No side effects were reported after treatment discontinuation.

The questionnaires showed that 19 of the 24 respondents were satisfied with the treatment, that three wished they had not received it, and that two were neither satisfied nor dissatisfied. Greater post-treatment growth was noted in patients who were dissatisfied.

Discussion

Our data suggest that high-dose 17β-estradiol was effective in reducing final height when started in premenarchal girls with CST. The mean reduction in final height was 2·4 ± 3·2 cm, in keeping with earlier studies reporting corrected and uncorrected reductions in the 2·1–10·0 cm range.[6,12,19,29] The mean age and bone age were rather advanced at start of treatment, a factor that may have contributed to the modest result. Furthermore, the result was less marked than expected because treatment was stopped at a bone age of 14 years which, a posteriori, was too early. Finally we used self-reported height, which has been shown to be well correlated with measured

height.[30,31] There is even a tendency in these studies to increase self-reported heights. In our study this would have reduced the apparent beneficial effect of the height reduction therapy. However, comparisons are hampered by differences across studies regarding baseline clinical features (most notably chronological age and bone age), treatment duration, therapeutic regimen (dose and nature of the oestrogen preparations) and the time of final height assessment.[28,32,33]

Skeletal maturation was significantly accelerated throughout the first treatment year in our study, and growth velocity decreased concomitantly. These data are consistent with *in vitro* evidence that high-dose oestrogens stimulate cartilage maturation without increasing growth velocity and that oestrogens accentuate the age-related decrease in chondrocyte size.[34,35]

Mean post-treatment growth was 3·3 ± 1·9 cm in our study, in agreement with previous data.[6,11,19,23] The cause of post-treatment growth is unclear. Mean bone age at treatment discontinuation in our study was 14 years. Conceivably, treatment was stopped before complete epiphyseal closure, allowing for subsequent growth. Alternatively, late pubertal completion of spinal growth may lead to an additional gain in stature after treatment discontinuation.[6]

The marked interindividual variability in final height reduction suggests that a subgroup of patients may derive greater benefit from treatment than the overall population. Our analysis of subgroups defined by the relation between bone age and chronological age at baseline, however, found no statistically significant differences were found regarding final height, growth reduction or post-treatment growth. Thus, one or more unknown factors may underlie the inter-individual variability in treatment efficacy; variations in oestrogen receptor behaviour may be among these factors.

No serious side effects were noted. Of 26 patients, 5 experienced fatigue, nausea, increased pigmentation, breast discomfort and/or abdominal pain. All side effects resolved after treatment discontinuation, and no thromboembolic events occurred. These findings support published data. High-dose ethinyl oestradiol or conjugated oestrogen therapy have been reported to cause adverse effects, most of which were mild and reversible. The adverse event rate may be dose-dependent.[20,33] Serious adverse events such as thromboembolism seem exceedingly rare.[36] Triglyceride elevation occurred in one of our patients but resolved after treatment discontinuation. Similarly, in earlier studies,[37,38] lipid changes proved reversible after treatment discontinuation. There was no evidence up to 2004 that high-dose oestrogen therapy causes long-term alterations in reproductive function.[1,39] A recent retrospective study of a large cohort of treated girls indicate an association with slightly impaired fertility in later life: treated women took longer to conceive and more required fertility services.[40] Spontaneous cyclical bleeding occurred in all but two patients within 6 months of treatment discontinuation. Others reported menarche within 1–6 months after the end of treatment, usually within the first month.[41] In our study, two patients were amenorrohoeic for 11 months after the treatment was stopped. Post-treatment amenorrhea lasting longer than 6 months after cessation of height-limiting oestrogen therapy occurred in about 5% of patients in an earlier study.[42]

No studies specifically designed to evaluate the side effects of high-dose 17β-estradiol therapy have been reported. Our sample size is too small to allow definitive conclusions regarding safety. Furthermore, we did not evaluate potential long-term side effects. The current uncertainty regarding the risk/benefit ratio of high-dose oestrogen height-limiting therapy should be borne in mind. In particular, whether oestrogen height-limiting therapy increases the risk of cancer of the breast or other sites remains unclear. In our study, a single patient reported breast discomfort, and no clinically significant breast disease was observed. This finding is in agreement with earlier studies.[1] However, long-term data on the breast cancer risk after high-dose 17β-oestradiol height-limiting treatment are not available.

We consider that the benefits from high-dose 17β-estradiol therapy in terms of height reduction were moderate. Furthermore, although high-dose 17β-estradiol seems safe in the short term, harmful long-term effects cannot be excluded. Nevertheless, 17β-estradiol therapy may deserve consideration in girls with a very tall predicted final height, no family history of breast cancer and no family or personal history of dyslipidaemia or coagulopathy.

New approaches to the pharmacological treatment of CTS in girls are needed. Drugs that influence GH secretion, such as the somatostatin analogues octapeptide and lanreotide, have been widely used to treat acromegaly for the last decade and have also been evaluated in CTS.[43,44] The GH receptor antagonist pegvisomant is being developed as an agent that antagonizes GH effects without acting on the pituitary gland or inhibiting GH secretion. This agent may prove an attractive alternative to oestrogens for final height reduction.[45] However, further studies are needed to assess this possibility.

In summary, our study shows that high-dose 17β-estradiol treatment is moderately effective in reducing the final height of girls with CTS. This treatment induces significant skeletal maturation and a decrease in growth velocity. The post-treatment growth in our patients may be ascribable in part to the fact that bone age was only 14 years at 17β-estradiol discontinuation. No serious side effects were noticed. Most of the patients were satisfied with the treatment. Nevertheless, the moderate treatment effect and the continuing uncertainty about the long-term safety of high-dose 17β-estradiol therapy indicate a need for caution. Research is needed to develop better height-limiting agents.

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