Oestrogen treatment of constitutional tall stature: a risk-benefit ratio

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Abstract

Oestrogens are given in high doses for the treatment of tall stature in girls. The aim of this study was to obtain data considering efficiency, side effects, and acceptance of the treatment of 50 constitutionally tall girls treated with conjugated oestrogens (7.5-11.25 mg/day). The mean (SD) adult height predictions were 188.3 (4.4) cm and the achieved height was 5.2 (3.3) cm less than the predicted height. A greater reduction from final predicted height occurred when treatment was started at an early bone age (<13.0 years) and with a remaining growth potential of greater than 10 cm. Even postmenarcheal girls, however, had a mean reduction of 4.8 (3.2) cm. The main side effects were considerable weight gain (>10 kg), an increase in triglyceride concentrations (37.5% of the patients), and increased platelet aggregation (60% of the patients). Altogether 84.6% of the patients were satisfied with the treatment and 15.4% regretted having had it.

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The first studies aiming to influence the growth of tall girls using oestrogens began in the 1940s with Albright and colleagues at the Massachusetts General Hospital in Boston. In 1956, Goldzieher published the first report on successful oestrogen treatment of tall girls.¹ Since then this treatment has been developed further and numerous studies have reported on new findings and therapeutic protocols.²⁻⁵ Various oestrogens have been used. Of these the conjugated oestrogens and ethinyloestradiol have gained the widest acceptance. Today there is widespread agreement that both steroids are equally efficacious. There does, however, seem to be differences with respect to their side effects. Some authors have claimed that the advantage of the conjugated oestrogens is their minimal adverse effects on coagulation.⁶⁻⁸ The effects of treatment have varied among girls when grouped on the basis of skeletal age, growth potential, diminution in growth rate, and/or advancement in skeletal age.^{3 4 9 10} Another subject of discussion is the effectiveness of treatment if started after menarche.^{3 9 11 12}

Undesirable effects have been noted and the risk-benefit ratio remains uncertain, especially with regard to the oncogenic potential of oestrogen administration^{2 13} and the risk for

thromboembolic disease.¹⁴⁻²⁴ This study, therefore is a further contribution in the clarification of the facts and may improve treatment by examining in greater depth three problem areas: effectiveness of treatment, factors affecting response to treatment, and side effects and risks.

Patients and methods

Between 1985 and 1994 50 constitutionally tall girls were treated with 7.5 to 11.25 mg/day of conjugated oestrogens in our endocrinological department. In some girls we used the higher dosage of 11.25 mg/day because of an advanced bone age at the onset of their treatment. To protect against the carcinogenic potential of oestrogens, a progesterone (lynestrenol) was given from the 20th until the 29th day of every month. None of the girls suffered from any other disease.

During treatment the girls were seen at three monthly intervals. They were examined, measured, weighed, side effects were noted, and blood samples were taken. Radiographs of the left hand, to assess bone age, were taken every six months. Measurements of the concentration of plasma lipids (cholesterol and triglycerides; Kodak Ektachem), liver enzymes (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, γ -glutamyltransferase, and alkaline phosphatase; Kodak Ektachem), glucose homeostasis (glycated haemoglobins HbA_{1c} and HbA₁; Bio-Rad Diamat), and haemostatic function tests were done. Anti-thrombin III was determined by radial immunodiffusion²⁵ using Partigen plates (Behring). Calibration curves were done with standard human plasma (Behring) and protein standard plasma (Behring). Partial thromboplastin time and thrombin time were determined by standard procedures with reagents provided by Behring. Fibrinogen was determined according to Clauss²⁶ and thrombocyte aggregation in platelet aggregation test III (PAT III) was tested.²⁷ These data were used to evaluate side effects. We obtained a retrospective view, by questionnaire, of side effects and their impact from the girls who concluded their treatment between 1991 and 1994.

Treatment was stopped at a bone age of 15.0 years (Greulich and Pyle²⁸). All height measures were made using the same stadiometer. To reduce variation every radiograph was assessed again by the same experienced reviewer. Final height was predicted using the tables of Bayley and Pinneau.²⁹ Height reduction was defined as the difference between the predicted height at the onset of treatment and the height achieved at the end of treatment.³⁰ All results are stated as mean (SD).

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Table 1 Data and results of 50 girls treated with conjugated oestrogens; values are mean (SD)

Chronological age (years)	12.8 (1.1)
Bone age (years)	12.0 (0.8)
Height at start of treatment (cm)	175.5 (3.7)
Predicted height at start (cm)	188.3 (4.4)
Final height prediction (cm)	183.0 (3.4)
Reduction of final height (cm)	5.2 (3.3)
Treatment period (months)	16.8 (4.2)

Results

Data and results are shown in table 1. The data show a final height reduction of 5.2 (3.3) cm. Skeletal maturation was accelerated by 1.8 years per year during treatment. The growth rate diminished throughout the treatment. The girls had a mean growth rate of 2.4 (1.6) cm during the first six months of treatment, 1.6 (0.9) during next six months, and 0.9 (0.5) during the 13th to 18th months.

The patients were subdivided into groups in relation to bone age, growth potential, and menarche before treatment to compare the effects of these different factors on the final height reduction. The data and results for these subgroups are shown in table 2. The mean reduction of final height increases when treatment is started at a bone age of <13.0 years and for a growth potential >10 cm (fig 1). In the group of 12 girls with menarche occurring before treatment, the effect on final height reduction was comparable with girls without menarche. These findings indicate that final height reduction closely correlates with bone age and growth potential at the onset of treatment, but not with the onset of menarche.

The evaluation of side effects is described in table 3. No serious side effects occurred. The major complaint was considerable weight gain. In 35 cases weight gain of more than 10 kg was registered. Nineteen girls complained of side effects, some of them of several symptoms at the same time. Thirty one girls had no clinical complaints. Liver enzymes were within the normal range. Glucose metabolism was also normal. Furthermore, cholesterol and triglycerides (fasting) were examined. For cholesterol there was no deviation from the norm, however triglycerides were increased in 37.5% of the patients, fluctuating between 1.6 and 2.6 mmol/l. With respect to coagulation, we found highly increased platelet aggregation in PAT III in 60% of the girls' profiles. All other coagulation parameters (thromboplastin time, partial thromboplastin time, fibrinogen, antithrombin III) were normal.

Two months after completion of treatment, a luteinising hormone releasing hormone test was performed. Hormonal concentrations of all girls were normal. The oestradiol plasma concentration as well as gonadotrophins showed that endogenous production of hormones had recommenced. Spontaneous cyclic bleeding occurred in all girls during the first six months after treatment.

From the questionnaire we found that 84.6% were grateful for having been treated and 15.4% regretted it; 38.4% recalled the side effects of treatment as unpleasant, 61.5% did not.

Discussion

The achieved height reduction of 5.2 (3.3) cm is in accordance with previously published data. The division of the patients into bone age subgroups confirmed height reduction is more pronounced if the bone age at the onset of treatment is at a young age (<13.0 years).^{2,3,9} In accordance with the observations of Normann and Bierich,^{4,6} we also found that the remaining growth potential clearly influenced the resulting height reduction. Whitelaw found no effective reduction of final height in pubertal girls after menarche.¹⁰ In our study the mean reduction of final height closely correlates with bone age and growth potential at the onset of treatment, but is independent of the time of menarche.

Serious side effects did not occur. Combining various studies, 1324 courses of treatment have been analysed with respect to side effects.^{2,3,6,12,13,31,32} Among the most common complaints were weight gain, transient nausea, headaches, striae, and calf cramps. The development of carcinoma has not been observed. Serious side effects seem to be very rare. The literature is short of studies demonstrating clinically significant effects of oestrogens on metabolism. Regarding the effects of high dose conjugated oestrogens on liver function, glucose tolerance and lipids, only triglycerides were found to be raised in our study.

During treatment with high doses of oestrogen, changes in the haemostatic system were observed which were similar to those known during treatment of women with oral contraceptives. Many authors also report a direct relationship between the dosage of oestrogen of the oral contraceptive and the risk of thrombosis. Oestrogens contained in oral contraceptives are ethinyloestradiol at a dosage of 20–50 µg/day or mestranol at a dosage of 50–100 µg/day. Two

Table 2 Data of 50 girls treated with conjugated oestrogens, divided according to bone age, growth potential, and menarche; values are mean (SD)

	Bone age (years) <12.0	Bone age (years) 12.0–13.0	Bone age (years) >13.0
No of girls	16	24	10
Reduction of final height (cm)	7.6 (3.4)	5.0 (2.2)	1.4 (1.3)
	Growth potential (cm) <10.0	Growth potential (cm) 10.0–15.0	Growth potential (cm) >15.0
No of girls	12	24	14
Reduction of final height (cm)	2.2 (2.2)	5.2 (2.4)	7.4 (3.6)
	Treatment after menarche	Treatment before menarche	
No of patients	12	38	
Chronological age (years)	12.5 (0.9)	12.9 (1.1)	
Bone age (years)	12.5 (0.8)	11.9 (0.7)	
Reduction of final height (cm)	4.8 (3.2)	5.2 (3.3)	

Table 3 Side effects of 50 girls treated with conjugated oestrogens

Side effects	Percentage of registrations
Weight gain >10 kg	70
Headache	14
Nausea	10
Striae	6
Calf cramps	6
Breast discomfort	6
Abdominal pain	6
Dysuria (without infection)	6
Hyperthermia	6
Oedema	6
Allergic skin reaction	6
Hypertension	2
Fatigue	2
Increased pigmentation	2

cases have been published of severe deep vein thrombosis during treatment of girls with tall stature with ethinyloestradiol.^{8,33} Blombäck *et al* observed lower concentrations of antithrombin III during treatment of tall stature with 250–1000 µg/day of ethinyloestradiol in all patients.¹⁴ Muntean and Borkenstein²³ observed with 500 µg/day ethinyloestradiol that all the factors of the prothrombin complex (factors II, VII, IX, X), fibrinogen, and platelet aggregation were increased.²⁴ Antithrombin levels were decreased. Further studies on the influence of oral contraceptives on coagulation confirm an increase of coagulation factors II, VII, IX, X, XII, of fibrinogen, protein C, and plasminogen, as well as a decrease of antithrombin III and of protein S.^{16,34,35} Petrykowski and Schmidt⁷ observed no decrease of antithrombin III during tall stature treatment with 7.5 mg conjugated oestrogens, and suggested that the conjugated nature of the oestrogen preparation accounted for this effect. Deficiency of antithrombin III is known to be associated with an increased risk of thrombosis.^{7,36,37} This leads to the question of whether ethinyloestradiol, used for both oral contraception and growth inhibition, causes greater changes leading to hypercoagulability than conjugated oestrogens. This presumption has been confirmed by these results. Platelet aggregation should be supervised during treatment. Further studies should

Figure 1 Final height reduction for each patient and corresponding bone age (years) at onset of treatment; in three girls there was no height reduction (one of 12.5 and two of 13.0 years bone age).

evaluate if a decreased dosage of oestrogens comparable with those in the contraceptive or hormone replacement preparations is still effective to reduce final height in constitutional tall stature girls with a lower amount of side effects.

Spontaneous menstruation occurred in all girls one to six months after discontinuation of treatment. These data are also in concordance with the other studies mentioned above, where the great majority of patients menstruated within the first three months after the end of treatment. However, there is the description of cases where post-therapeutic amenorrhea lasted up to 13 months.³² Later fertility was not affected. Wettenhall *et al*,⁵ Crawford,³¹ and Prader and Zachmann³² found that patients had normal number of children.

Conclusion

We conclude that when starting treatment for girls with tall stature at a bone age of <13.0 years and with a growth potential of >10 cm, satisfactory results, with an average reduction of 5.2 cm, will be achieved. Menarche before the onset of treatment is not detrimental to a successful height reduction. Only minor side effects were observed during treatment. The great majority of the girls expressed their satisfaction with the treatment. The good acceptability of conjugated oestrogens, especially regarding their minimal effects on metabolism and haemostasis, has been shown.

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