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ORIGINAL ARTICLE

Oestrogen treatment for tall stature in girls: estimating the effect on height and the error in height prediction

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Summary

Objective To determine the effect of oestrogen treatment on attenuating the growth of tall girls after adjusting for error in height prediction.

Design Retrospective cohort study.

Patients Tall girls assessed by Australian paediatric endocrinologists between 1959 and 1993. A total of 279 girls received oestrogen treatment (diethylstilboestrol or ethinyl oestradiol) and 367 girls were assessed but not treated.

Measurements Estimated mature height (EMH) was calculated using radiographic assessment of bone age in adolescence. Final adult height was self-reported at follow-up. To control for error in the EMH predictions and their different distributions by treatment status, pairs of treated and untreated girls, matched on EMH within 1 cm, were selected for analysis. Covariate adjusted estimates of treatment effect (final height – EMH) were calculated.

Results In the sample of 108 matched pairs, the mean difference between the final height and EMH was –1·4 cm (SE 0·29) in the treated group and 1·1 cm (SE 0·23) in the untreated group, giving an unadjusted treatment effect of –2·5 cm (95% CI –3·2 to 1·8). A regression model based on 107 pairs of treated and untreated girls contained a significant interaction between bone age at treatment initiation and treatment, which estimated an approximately 1 cm per year decrease in treatment effect. The treatment effect was greatest in those commencing treatment at an early bone age and was significant if initiated before a bone age of 15 years.

Conclusions On average, oestrogen treatment resulted in an adult height that was less than predicted. Although treatment was more effective in the least mature girls, the mean height difference was relatively modest for most treated girls.

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Introduction

Oestrogen treatment to reduce the adult height of constitutionally tall girls was first reported in 1956[1] and has been used for psychosocial indications since then. The oestrogens most commonly administered have been diethylstilboestrol (DES), ethinyl oestradiol (EE) and conjugated oestrogens. The use of oestrogens is based on the knowledge that, in normal pubertal development, oestrogen leads to the epiphyseal fusion of the long bones. Moderately high doses of oestrogen have been used, usually 3–10 times daily oestrogen requirements for young adult women. Estimated mature height (EMH) is generally determined based on bone age and height predicted by the Bayley–Pinneau tables.[2]

Treatment has been considered for tall girls with EMH values of more than 2 or 2·5 standard deviations above the population mean[3–5] or of more than 183 cm in some recent series.[6] A survey of paediatric endocrinologists in the USA in 2002 found that 33% of 411 respondents offered treatment of tall stature and 23% had treated tall girls in the preceding 5 years, although most had treated less than five girls.[6] Controversially, oestrogen treatment has recently been proposed as a therapeutic option to attenuate the growth of children with profound developmental disabilities,[7] a measure intended to make care-giving easier when children reach adult size. Treatment is associated with a range of short-term adverse effects[4,6] and with impaired fertility in the long term.[8]

Estimates of the effectiveness of treatment in reducing adult height have varied widely and reports of effects in small study samples continue to appear in the literature.[9] Differences in the height prediction models used, the treatment regimens, and developmental maturity of girls at the time of commencing treatment are thought to explain much of the variability.[4] Most studies have been small, with only two reporting outcomes in more than 100 treated tall girls.[10,11] In a review of 17 studies, Drop *et al*. reported estimates of height reduction ranging from 2·1 to 10 cm.[4] The majority of studies suggested a greater effect on height reduction when treatment commenced at an early bone age. Error in height prediction (predicted EMH – final height) is well recognized but few studies have taken it into account when estimating the effect of treatment. Nine studies of untreated constitutionally tall girls[4] reported height prediction errors ranging from +2·4 to –1·0 cm, with greater prediction accuracy observed in

older girls. All but one of these studies ($n = 88$)[11] included fewer than 30 girls.

We conducted a follow-up study of long-term health and psychosocial outcomes in a large cohort of Australian tall girls who were treated or assessed for tall stature between 1959 and 1993.[8,12,13] Here we report on the effect of treatment on final height after adjusting for bias in the height prediction model and the influence of other growth and development factors.

Methods

Study sample

The study included tall girls who were assessed or treated in Australia and who were identified from original medical records; a subsample of the complete cohort we reported on previously.[8] The majority (95%) were identified from the medical records of one paediatric endocrinologist who saw patients between 1959 and 1993. Girls whose parents had sought a medical opinion about their tall stature and who had had a radiological assessment (hand and wrist X-ray) of their bone age were eligible to participate. They included girls who received oestrogen treatment to reduce their adult height (treated group) and those who did not (untreated group). Girls with a predicted height of greater than 177 cm were generally considered to be eligible for treatment.[3] The main reasons why girls did not have treatment were: family preference, the girl's predicted adult height did not warrant treatment, or the girl had limited remaining growth potential at the time of assessment.

Women were traced with the use of electoral rolls and telephone listings, then contacted by mail and invited to participate. Nonrespondents were followed up by mail and by telephone. Written informed consent was obtained from all study participants. The study had the approval of the La Trobe University Human Ethics Committee.

Data collection

Information on chronological age, bone age, height, EMH and Tanner stage (breast and pubic) was abstracted from medical records made at the time of the initial and last assessments. The last assessment was the assessment immediately before treatment began in the treated group, and, in the untreated group, the last recorded assessment if more than one had been performed. Data on final height were collected by postal questionnaire at follow-up. Participants were asked to measure their height before noon and in bare feet, standing on a hard floor without carpet. They were asked to stand straight and stretched with their backs against a wall, to place a picture frame or similar firm square or rectangular object on their head, and to draw a mark on the wall immediately below the frame edge. It was requested that they measure the height from the floor to the mark with a tape measure and to repeat the process as a check.

Height prediction

Height in adolescence was measured according to standard protocols using a modified Baldwin square[14] or a Harpenden stadiometer.[15] Bone age was determined using radiographs of the wrist and the Greulich–Pyle atlas.[16] Bone age was calculated by a single observer for at least 95% of girls in the study. EMH was calculated using the Bayley–Pinneau tables, which provide estimates of final adult height for normal girls according to their height and bone age.

Treatment regimens

Until 1971, the most common treatment in Australia was with DES at 3 mg daily. Later, EE was the treatment of choice at a dose of 150 μg daily, starting at 50 μg per day in the first week and progressing to 100 μg per day in the second week.[15] Progestogen was given as norethisterone, 5 mg twice daily for 4 days at monthly intervals, to ensure cyclical bleeding. Treatment was generally continued for around 2 years, determined by slowed growth.

Obtaining the matched sample

A major problem was encountered when examining the difference between EMH and final height in the 647 girls in the total sample. Girls who did not receive treatment had an estimated mature height that was, on average, 1·86 cm less than their final height and, in the treated group, girls had an estimated mature height that was, on average, 2·13 cm more than their final height. To account for the error in the Bayley–Pinneau estimates of EMH, we performed a matched-pairs analysis. To do this, we matched one subject from the treated group with one from the untreated group according to their EMH to the nearest whole unit. For example, for an untreated woman with an EMH of 180 cm, we randomly selected a woman from the treated group who also had an EMH of 180 cm. By performing this randomized matching, we were able to obtain an exact match on EMH for 108 of the 279 treated subjects. We were unable to obtain an exactly matched untreated subject for the other 171 treated subjects as they tended to be taller than the untreated subjects.

Statistical methods

Analyses were performed using STATA version 9·2. Descriptive statistics computed included means and standard errors. Paired *t*-tests were used to compare treatment group differences. The outcome variable was defined as height difference, calculated as final height minus EMH. A multivariable regression model clustering on matched pair was used to obtain a covariate adjusted estimate of treatment effect.

Results

A comparison of eligible women who did and did not participate in the study showed that participants had a mean EMH of 176·24 (SD 5·1) cm and nonparticipants had a mean EMH of 175·13 (SD 4·93) cm. Although this difference was statistically significant ($P < 0·001$), it was small in absolute terms and suggests that recruitment bias was not a significant problem. The characteristics of matched treated and untreated girls were compared and paired *t*-tests performed (Table 1). Treated and untreated girls were similar in mean chronological age and height at last assessment. Treated girls

Table 1. Estimated means and standard error for all matched subjects, untreated and treated groups, and *P*-value for paired *t*-test of mean difference

	Untreated		Treated			
	N	Mean (SE)	*N*	Mean (SE)	Paired mean difference	*P*
Chronological age (years)	107	13·3 (0·15)	107	13·2 (0·12)	0·2 (0·18)	0·27
Bone age (years)	107	13·5 (0·13)	107	13·2 (0·09)	0·3 (0·16)	0·06
Height at last assessment* (cm)	106	172·0 (0·55)	106	171·4 (0·50)	0·9 (0.66)	0·16
Breast Tanner	105	3·9 (0·11)	102	3·4 (0·10)	0·5 (0·16)	< 0·01
Pubic Tanner	105	4·1 (0·10)	102	3·5 (0·10)	0·6 (0·14)	< 0·01
Final height (cm)	108	179·9 (0·34)	108	177·5 (0·33)	2·4 (0·36)	< 0·01
Height difference† (cm)	108	1·1 (0·23)	108	–1·4 (0·29)	2·4 (0·36)	< 0·01

*Height at last assessment before treatment commenced in the treated group, last recorded assessment in the untreated group.
†Height difference = final height – estimated mature height (EMH).

Table 2. Fitted linear regression model in the matched data

	Coefficient	Std error	*T*	*P*	95% CI
Treatment	–15·85	6·71	–2·36	< 0·020	–29·16 to –2·54
Breast Tanner score	–0·44	0·21	–2·05	0·043	–0·87 to – 0·01
Bone age	0·14	0·23	0·63	0·53	–0·31 to 0·59
Bone age × treatment	0·98	0·49	1·98	0·05	0·00–1·97
Intercept	0·77	3·02	0·25	0·80	–5·23 to 6·78

Number of matched pairs = 107, $F(4,106) = 20{\cdot}90$, $P < 0{\cdot}001$, $R^2\% = 26{\cdot}2$.

were less mature than untreated girls with a less advanced mean bone age ($P = 0{\cdot}06$) and significantly lower breast and pubic Tanner scores ($P < 0{\cdot}01$). Practice differed little over time, with no significant difference seen in bone age by year of commencing treatment. The mean duration of treatment was 2·02 (SD 0·62) years in the DES-treated group and 1·86 (SD 0·50) years in the EE-treated group. Treated girls were significantly different from untreated girls in their final height and height difference (final height – EMH) ($P < 0{\cdot}01$). Treated girls had a mean height difference of –1·4 (SE 0·29) cm. Those treated with DES appeared to have a greater height difference (–1·8 cm, SE 0·43) than EE-treated girls (–1·2 cm, SE 0·41) but the difference was not statistically significant ($P = 0{\cdot}29$). Although treated girls, on average, had a smaller final height than their EMH, the final height of untreated girls was, on average, greater than their EMH prediction (height difference 1·1 cm, SE 0·23), thus demonstrating that the Bayley–Pinneau method underpredicted EMH in this sample of girls.

The results of the regression analysis of the matched data are shown in Table 2. Initial regression analyses showed that eight subjects with a breast Tanner score of 1 (four treated and four untreated) were overly influential on the estimates of the effect of breast Tanner score and bone age. These eight subjects, but not their matches, were therefore excluded from the analysis. As a result of this and some missing values, data were available for 199 subjects in 107 pairs. This analysis yielded a model with treatment, breast Tanner stage and bone age and a bone age treatment interaction having significant effects on height difference. Bone age-specific estimates of treatment effect are plotted in Fig. 1 along with 95% confidence limits. The figure shows that the treatment effect (measured by the difference in final height – EMH between treated and untreated subjects of a specific bone age) is significant, zero is contained within the confidence limits, if treatment was initiated before a bone age of 15 years. The estimated treatment effect is approximately a 6 cm height difference when treatment is initiated at a bone age of 10 years and the effect is estimated to decrease at a rate of approximately 1 cm per year.

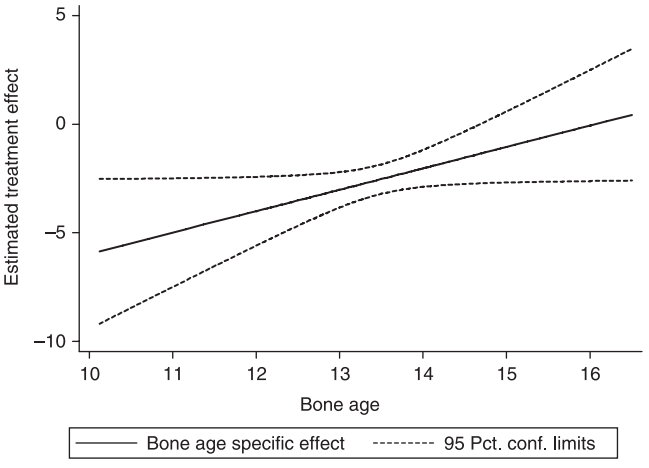

Fig. 1 Bone age-specific estimated treatment effect with 95% confidence limits from the fitted regression model in Table 2.

Discussion

In the absence of findings from a randomized controlled trial of the effectiveness of oestrogen treatment to reduce the adult height of tall girls, we have to rely on data from observational studies. Findings from this study indicate that oestrogen treatment for tall stature resulted in a final height that was on average less than the height predicted in adolescence, but the treatment effect was more modest than many previous studies have suggested. The treatment regimens and timing reflected common clinical practice over several decades when growth-limiting therapy was most common. This study had the advantage of a large comparison group of untreated tall girls that allowed for an assessment of the error involved in estimating the mature heights of tall girls and showed that the prediction method tended to underestimate final height in the untreated group. Few other studies have attempted to take height prediction error into account when estimating the effect of treatment. The analysis of pairs of treated and untreated girls matched on EMH is novel, and it explicitly controlled for bias in the EMH predictions that was associated with the height predicted. The regression model allowed us to estimate the effect of treatment with further adjustment for the independent effects of bone age and breast Tanner stage on height difference (final height – EMH). In the absence of appropriate untreated comparison groups, previous estimates of the effectiveness of treatment are likely to have been inaccurate.

A limitation of our study was its reliance on women's self-reported final height in the follow-up questionnaire. While self-reported height tends to be overestimated in samples of the general population, taller women report height more reliably than shorter women,[17] and height is a highly salient characteristic for women with a history of assessment or treatment for tall stature. At the time of follow-up, women were residing in many different parts of Australia and in other countries, and accurate measurement of final height was not feasible. Although we can expect there to have been some error in self-reported heights, our estimate of treatment effectiveness would be biased only if the error was systematically different in the treated and untreated groups.

The observation that treatment effectiveness was greatest in girls with the least advanced bone age is consistent with findings from other studies.[4] High-dose oestrogen treatment induces breast development and menstrual bleeding in girls who are prepubertal or in the early stages of puberty, and therefore, while treatment is more likely to be effective, it is generally not recommended for use in girls aged less than 11 years. The growth-attenuating effects of treatment also have to be weighed against the demonstrated short-term risks of treatment[4,6] and its association in the long term with impaired fertility.[8] Not surprisingly, girls in this study with only modest height reduction were also more likely to be dissatisfied with the treatment in the long term.[12]

This is one of the few studies to have estimated the effect of treatment on height in a large sample of treated girls with appropriate adjustment for bias in the height prediction model for estimating mature height. Together with evidence of short- and long-term health risks associated with treatment, these findings on treatment effectiveness help to provide a better basis for counselling concerned tall girls and their parents, and for more informed decision making about treatment.

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