Oestrogen treatment to reduce the adult height of tall girls: long-term effects on fertility

Alison Venn, Fiona Bruinsma, George Werther, Priscilla Pyett, Donna Baird, Penelope Jones, Jo Rayner, Judith Lumley

Lancet 2004; 364: 1513–18

Menzies Research Institute, University of Tasmania, Private Bag 23, Hobart 7001, Australia (A Venn PhD); **Mother and Child Health Research, La Trobe University, Victoria, Australia** (F Bruinsma M App Sci, P Pyett DHSc, P Jones Grad Dip Epid, J Rayner MWH, Prof J Lumley FFPH); **Centre for Hormone Research, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia** (Prof G Werther MD); **and National Institute of Environmental Health Sciences, North Carolina, USA** (D Baird PhD)

Correspondence to:
Dr Alison Venn
Alison.Venn@utas.edu.au

Summary

Background **Treatment with oestrogen to reduce the adult height of tall girls has been available since the 1950s. We undertook a retrospective cohort study to assess the long-term effects of this treatment on fertility.**

Methods **Eligible participants were identified from the records of Australian paediatric endocrinologists who assessed tall girls from 1959 to 1993, and from self-referrals. Individuals included girls who had received oestrogen treatment (diethylstilboestrol or ethinyl oestradiol) (treated group) and those who were assessed but not treated (untreated group). Information about reproductive history was sought by telephone interview.**

Findings **1432 eligible individuals were identified, of whom 1243 (87%) could be traced. Of these, 780 (63%) completed interviews: 651 were identified from endocrinologists' records, 129 were self-referred. Treated (n=371) and untreated (n=409) women were similar in socioeconomic and other characteristics. After adjustment for age, treated women were more likely to have ever tried for 12 months or more to become pregnant without success (relative risk [RR] 1·80, 95% CI 1·40–2·30); more likely to have seen a doctor because they were having difficulty becoming pregnant (RR 1·80, 1·39–2·32); and more likely to have ever taken fertility drugs (RR 2·05, 1·39–3·04). Time to first pregnancy analysis showed that the treated group was 40% less likely to conceive in any given menstrual cycle of unprotected intercourse (age-adjusted fecundability ratio 0·59, 95% CI 0·46–0·76). These associations persisted when self-referred women were excluded.**

Interpretation **High-dose oestrogen treatment in adolescence seems to reduce female fertility in later life. This finding has implications for current treatment practices and for our understanding of reproductive biology.**

Introduction

The use of oestrogens to reduce the adult height of tall girls dates back to the 1950s[1] and has been used in Europe, Australia, and the USA.[2–6] The practice is based on the knowledge that in healthy pubertal development, oestrogen leads to the epiphyseal fusion of the long bones. In girls with expected heights of more than 177 cm (or 183 cm in some series), such treatment has been available for psychosocial indications.[7–9] The number of girls treated in recent years is less than in the 1960s–1980s, probably because of greater social acceptance of tall female stature. A recent survey of US paediatric endocrinologists[2] recorded that 96 (23%) of 411 respondents had treated tall girls in the preceding 5 years, though most had treated fewer than five girls.

The oestrogens most commonly used to treat such girls are ethinyl oestradiol (EE) and conjugated oestrogens.[2,9] Before 1971, diethylstilboestrol (DES) was also used[7,8] but was discontinued because of reports that in-utero exposure was associated with clear-cell adenocarcinoma of the vagina in the daughters of women who were treated in pregnancy to prevent miscarriage.[10] Progestagens (in addition to oestrogens) are generally used for several days each month to induce cyclical bleeding. The effectiveness of treatment is uncertain[9] with height reductions of 2·1 to 10 cm being reported. There have been no randomised controlled trials of treatment effectiveness.

Short-term side-effects of oestrogen treatment for tall stature include menstrual irregularities, weight gain, nausea, deepened pigmentation of the nipples and areolae, night cramps, limb pains, galactorrhoea, benign breast disease, excessive vaginal discharge, thrombosis, and ovarian cysts.[2,3,8,9,11] Little is known about the long-term effects of treatment. De Waal and colleagues[6] reported menstrual characteristics and reproductive outcomes for treated and untreated women in the Netherlands. Outcomes seemed normal, but the sample size was small and the average follow-up was only 10 years after treatment. Our aim was to assess long-term health and psychosocial outcomes in a large cohort of Australian tall girls. We report on the effect of exposure to high-dose oestrogens in adolescence on subsequent fertility.

Methods

Participants

We identified individuals from the medical records of Australian paediatricians who assessed or treated tall girls from 1959 to 1993, and from self-referrals. Women whose parents had sought a medical opinion about their tall stature and who had had a radiological assessment (hand and wrist radiography) of their skeletal age were eligible to participate. They included girls who had received oestrogen treatment (3 mg DES daily or 150 μg EE daily) in adolescence to reduce their adult height (treated group) and those who had not (untreated

group). The most common reasons for not having had treatment were because the girl's predicted adult height did not warrant treatment, or because the girl had little remaining growth potential at the time of assessment.

We identified most women through the records of one paediatric endocrinologist. Other treating doctors (n=50) were identified through professional networks and by treated women. Three were able to identify eligible participants. The remainder did not assist because they were deceased or unwell (n=11), no longer had records, could not readily identify eligible individuals (n=25), were unwilling to assist (n=2), or they could not be contacted (n=9). Women who self-referred to the study included members of an advocacy group known as Tall Girls Inc and women who contacted us directly as a result of publicity about the study.

Data collection

We traced women through electoral rolls and telephone listings, then contacted them by mail and invited them to complete a postal questionnaire and computer assisted telephone interview. Non-respondents were sent a reminder letter and called by telephone. The postal questionnaires sought demographic information and details of assessment and treatment. The interview included questions about reproductive history (including pregnancies and their outcomes), fertility problems, and sexual history. Data were obtained from medical records, if available, for those women who provided consent. Data items retrieved included age at menarche; treatment type, dose, and duration; and details of first and last assessments of estimated mature height. Bayley and Pinneau's method[12] had been used to calculate estimated mature height. The study received ethics committee approval and participants gave written informed consent.

Measures of fertility

We used two approaches to investigate the relation between treatment and subsequent fertility. First, we asked women to answer yes or no to whether they had ever tried for 12 months or more to become pregnant without succeeding, whether they had ever seen a doctor because of trouble becoming pregnant, and whether they had ever taken fertility drugs for the treatment of infertility. Women who reported that they had seen a doctor because of difficulty conceiving were asked whether any of the following investigations had been undertaken: temperature charting, hormone test, post-coital mucus test, hysterosalpingogram, endometrial biopsy, or laparoscopy. Participants were asked about any diagnosis they had been given as a result of these investigations.

The second approach was to analyse time to pregnancy with the outcome being pregnant or not pregnant for each month of attempting pregnancy. Women who had at least one pregnancy were asked to estimate the number of months of unprotected intercourse before they became pregnant with their first pregnancy, irrespective of pregnancy outcome. Women who indicated that when they became pregnant they were "trying not to get pregnant" (ie, using contraception or abstaining from intercourse) were excluded from the time to pregnancy analysis. Cycles were censored at 12 months, since 1 year of trying to get pregnant without success corresponds to the clinical definition of infertility, and medical interventions might have affected results beyond that point.[13]

Statistical methods

Stata software (version 8), was used for all statistical analyses. The differences between treated and untreated women were investigated using the t test for continuous data, and the χ^2 test for categorical data. To account for possible confounders, multivariable log binomial regression was used to estimate adjusted relative risks. A p value less than 0·05 was judged to be significant.

For time to pregnancy analysis, Weinberg et al[13] proposed a discrete survival time model that yields estimates of a fecundability ratio (FR) which is the monthly rate of conception in women exposed to treatment divided by that in the unexposed. This model might be fitted using the exact partial likelihood for the Cox proportional hazards model which accounts for the numerous ties that occur. All models included age at the time of first attempting conception. Other potential confounding variables (adult height, body-mass index, smoking, recent oral contraceptive use before conception was attempted, number of sexual partners, age at first intercourse, and frequency of intercourse at the time of conception) were entered into the model one at a time and retained if their presence significantly improved the fit by the likelihood ratio criterion or if their presence in the model modified in any important way the point estimate for the effect of exposure to treatment. Unadjusted survival curves were constructed with the Kaplan-Meier method. Treated and untreated groups were compared with the log-rank test.

Role of the funding source

The National Health and Medical Research Council (Australia) funded the study but had no role in its design, analysis, or interpretation, or in data collection or writing of the report.

Results

Characteristics of study participants

A cohort of 1432 eligible participants was identified: 1248 from medical records (1222 of these from one paediatric endocrinologist) and 184 from self-referrals. 572 women in the cohort were treated and 860 women were untreated. 1243 (90% of treated and 84% of

untreated) were traced and invited to participate in the study: of these, 398 treated and 448 untreated women agreed. Data for reproductive history were available for 371 treated women (72% of those traced) and 409 (56%) untreated women. Written consent to extract data from medical records was provided by 93% (n=726) of women who completed the interview. However, medical records were available for only 618 (75% of treated and 95% of untreated).

Characteristic	Treated group (n=371)	Untreated group (n=409)
Age (years)		
<25	3 (0·8%)	6 (1·5%)
25–34	88 (23·7%)	120 (29·3%)
35–44	179 (48·3%)	239 (58·4%)
45–54	95 (25·6%)	44 (10·8%)
>54	4 (1·1%)	0
Data missing	2 (0·5%)	0
Marital status		
Married or cohabiting	281 (75·7%)	308 (75·3%)
Divorced, separated, or widowed	43 (11·6%)	33 (8·1%)
Single	43 (11·6%)	68 (16·6%)
Data missing	4 (1·1 %)	0
Highest education level achieved		
Did not complete secondary school	36 (9·7%)	21 (5·1%)
Completed secondary school	61 (16·4 %)	73 (17·9%)
Apprenticeship/certificate/diploma	84 (22·7 %)	88 (21·5%)
Degree	106 (28·6%)	144 (35·2%)
Postgraduate	82 (22·1 %)	82 (20·1%)
Data missing	2 (0·5%)	1 (0·2%)
Estimated mature height (cm)*		
⩽177·0	70 (18·9%)	292 (71·4%)
177·1–182·9	175 (47·2%)	97 (23·7%)
⩾183·0	118 (31·8%)	12 (2·9%)
Data missing	8 (2·2%)	8 (2·0%)
Adult height (cm)†		
⩽177·0	109 (29·4%)	200 (48·9%)
177·1–182·9	211 (56·9%)	174 (42·5%)
⩾183·0	50 (13·5 %)	35 (8·6%)
Data missing	1 (0·3%)	0
Smoking		
Ever smoked	195 (52·6%)	213 (52·1%)
Never smoked	172 (46·4%)	196 (47·9%)
Data missing	4 (1·1%)	0
Oral contraceptive use		
Ever used	352 (94·9%)	390 (95·4%)
Never used	17 (4·6%)	18 (4·4%)
Data missing	2 (0·5%)	1 (0·2%)
Years of oral contraceptive use		
<1	119 (32·1%)	106 (25·9%)
1–5	97 (26·2%)	102 (24·9%)
6–10	57 (15·4%)	76 (18·6%)
11–15	44 (11·9%)	60 (14·7%)
>15	36 (9·7%)	47 (11·5%)
Data missing	18 (4·9%)	18 (4·4%)
Age at first sexual intercourse (years)		
<16	57 (15·4%)	49 (12·0%)
16–19	219 (59·0%)	262 (64·1%)
20–29	82 (22·1%)	84 (20·5%)
>29	5 (1·3%)	6 (1·5%)
Data missing	8 (2·2%)	8 (2·0%)
Lifetime number of male sexual partners		
0	4 (1·1%)	3 (0·7%)
1	64 (17·3%)	61 (14·9%)
2	31 (8·4%)	37 (9·1%)
3–5	79 (21·3%)	97 (23·7%)
6–10	93 (25·1%)	95 (23·2%)
11–20	54 (14·6%)	69 (16·9%)
>20	38 (10·2%)	31 (7·6%)
Refused to answer	5 (1·4%)	11 (2·7%)
Data missing	3 (0·8%)	5 (1·2%)

*Derived from medical record at first assessment (n=662) or self-report (n=102).
†Self reported.

Table 1: **Characteristics of study participants**

The characteristics of study participants are shown in table 1. The mean age of participants was 39·8 years (range 20–55) in the treated group and 37·7 years (23–54) in the untreated group. Treated and untreated participants were similar in their marital status and highest level of education achieved. Self-reported current height was greater in treated women (mean 179·0 cm, SD 4·0) than in untreated women (176·8 cm, 4·9 cm). Similarly, the first recorded estimated mature height was greater in the treated women (181·5 cm, 6·3 cm) than in those untreated (174·3 cm, 4·6 cm). Both groups were very similar in their history of smoking, oral contraceptive use, age at first sexual intercourse, and lifetime number of male sexual partners.

A comparison of eligible individuals according to whether or not they completed an interview showed that non-participants (n=606 excluding 46 with missing data) were similar in age (mean 39·0 years) to participants (mean 39·1 years). However, estimated mature height at first assessment was lower in non-participants (175·1 cm) than in participants (176·3 cm, p<0·001).

Oestrogen treatment

Women treated with DES (n=151; five of whom were treated with both DES and, later, EE) were similar to those treated with EE (n=195) in terms of their age at the start of treatment (DES 12·7 years, EE 13·1 years), estimated mature height predicted before treatment (DES 182·4cm, EE 182·8cm) and the duration of treatment (DES 26·4 months, EE 23·5 months). The type of oestrogen given was unknown for 25 women. Treatment commenced before menarche in 50% of DES treated and 55% of EE-treated girls. In addition to oestrogens, progestagens such as medroxyprogesterone acetate were routinely administered as 5 mg twice daily for 4 days every month.

	Treated n=371	Untreated n=409	Adjusted RR* (95% CI)
Ever tried for ⩾12 months to become pregnant without succeeding	133 (35·9%)	76 (18·6%)	1·80 (1·40–2·30)
Ever seen a doctor because of trouble becoming pregnant	127 (34·2%)	73 (17·9%)	1·80 (1·39–2·32)
Ever taken fertility drugs	68 (18·3%)	34 (8·3%)	2·05 (1·39–3·04)
Ever been pregnant	287 (77·4%)	313 (76·5%)	0·93 (0·87–0·99)
Ever had livebirth	248 (66·9%)	267 (65·3%)	0·87 (0·79–0·95)

*Adjusted for current age. Data are n (%) unless otherwise indicated.

Table 2: **History of fertility problems by treatment status**

	Treated % (n=127)	Untreated % (n=73)	p
Investigations			
Charted temperature	85 (66·9%)	35 (48·0%)	<0·01
Hormone test	88 (69·8%)	52 (71·2%)	0·83
Postcoital mucus test	30 (23·6%)	11 (15·1%)	0·12
Hysterosalpingogram	55 (43·3%)	24 (32·9%)	0·14
Endometrial biopsy	26 (20·5%)	9 (12·3%)	0·13
Laparoscopy	80 (63·0%)	38 (52·1%)	0·09
No investigations	12 (9·5%)	6 (8·2%)	0·76
Data missing	1 (0·8%)	0	..
Diagnoses			
Ovulatory problem	36 (28·4%)	22 (30·1%)	0·70
Tubal problem	25 (19·7%)	11 (15·1%)	0·41
Uterine problem	11 (8·7%)	8 (11·0%)	0·59
Male factor	27 (21·3%)	15 (20·6%)	0·91
Endometriosis	8 (6·3%)	3 (4·1%)	0·51
Other causes	6 (4·7%)	5 (6·9%)	0·53
Unexplained	23 (18·1%)	9 (12·3%)	0·28
No diagnosis	27 (21·3%)	22 (30·1%)	0·20
Missing	1 (0·8%)	0	..

Table 3: **Infertility investigations and diagnoses in women who had seen a doctor because they were having trouble becoming pregnant, by treatment for tall stature**

Fertility problems

Women who had been treated with oestrogens to reduce their adult height were more likely to report fertility problems than were untreated women (table 2). This finding was evident for those who had tried for 12 months or more to become pregnant without success, those who had ever seen a doctor because of trouble becoming pregnant, and those who had ever taken fertility drugs. Among women who had ever taken fertility drugs, the total number of fertility drug cycles was similar for both groups. After adjustment for age, treated women were less likely to have ever been pregnant (table 2), and to have ever had a live birth. Although treated women tended to be taller than untreated women, at first assessment and in adulthood, differences in height did not explain the association of treatment with fertility problems: reduced fertility among the treated remained when height was included in the model, and height was not related to fertility problems in the untreated. This was true for estimated mature height as well as adult height. None of the other potential confounders substantially altered the results.

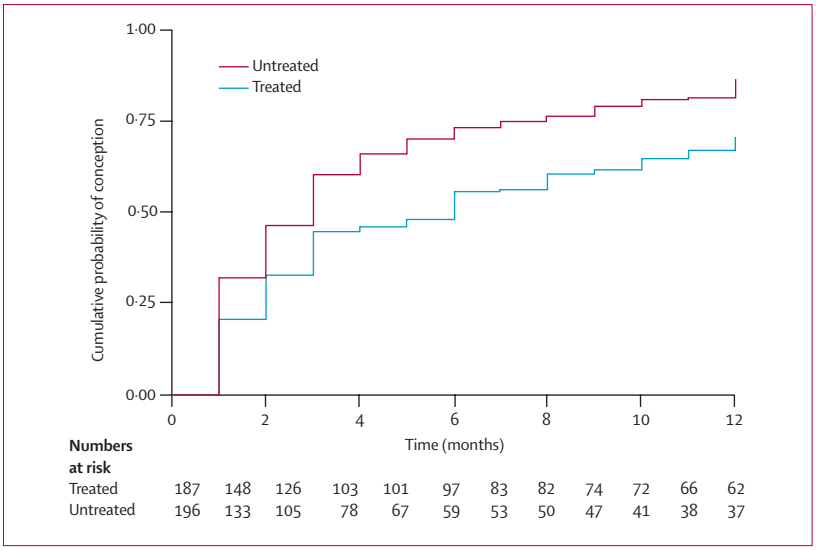

Figure: **Kaplan-Meier curves, estimating cumulative conception probabilities for untreated and treated tall girls attempting a first pregnancy**

Because of the possibility that women with a history of fertility problems might be over-represented among those who self-referred to the study (n=111 treated women, n=18 untreated women), the risk estimates were re-calculated after self-referred participants were excluded. Evidence of an increased risk of fertility problems in the treated group remained for having ever tried for 12 months or more to become pregnant without success (RR 1·69, 95% CI 1·29–2·23), having ever seen a doctor because of trouble becoming pregnant (1·77, 1·33–2·34), and having ever taken fertility drugs (1·93, 1·25–2·98). Another poor reproductive outcome, miscarriage, was not significantly more likely to be reported by women in the treated group (26%) compared with the untreated (23%) (adjusted RR 1·05, 95% CI 0·82–1·35), suggesting that treated women were not reporting more reproductive problems in general.

The response rate in the treated group was higher (72%) than in the untreated (56%), and treated women with reproductive problems may have been more interested in participating. A sensitivity analysis was done to see if such a selective response could explain whether the increased infertility we recorded was associated with treatment (the observed unadjusted RR was 1·93, 95% CI 1·51–2·46). First, we assumed that treated non-participants had, like the untreated women, a prevalence of infertility of 18·6%. This prevalence is similar to that reported in a recent population-based survey[14] of 8988 Australian women aged 16–59 years, which noted that 15·5% of women had had difficulty conceiving. When this hypothetical group of non-participants was added to the analysis, the estimated treatment effect was still highly significant (RR 1·61, 95% CI 1·33–1·94). Then we tested the worst-case scenario: we assumed that the treated non-participants had no infertility (all were able to conceive within 12 months). Even after including this hypothetical group of non-participants in the analysis, a significant, though weaker, treatment effect remained (1·25, 1·02–1·53). Selective non-response of women with low fertility in the untreated group would also suggest increased infertility in the treated women. When we assumed that untreated non-respondents had the same prevalence of infertility as the treated respondents (35·6%), a significant treatment effect still remained (1·3, 1·10–1·50).

Cause of fertility problems

Most women (89% treated, 92% untreated) who had seen a doctor because of difficulty conceiving reported having had one or more infertility investigations

(table 3). The only investigation to have been significantly more common in the treated group was temperature charting, a practice that has become infrequent in recent years. This finding might indicate the older mean age of treated girls and practices that were common at the time they were having fertility problems. The causes of infertility reported by women in both groups were similar.

Time to pregnancy

For those attempting a first pregnancy, the probability of conception every month was markedly lower for treated compared with untreated women (log rank test p<0·001) (figure). Time to pregnancy analysis excluded 166 women who conceived their first pregnancy while they were reportedly trying not to get pregnant (22% in the treated group, 21% in the untreated). The age-adjusted per cycle rate of conceiving a first pregnancy in women who were treated for tall stature was significantly less than that in the untreated group with an FR of 0·59 (95% CI 0·46–0·76). Other potential confounding variables (adult height, estimated mature height, body-mass index, smoking, recent oral contraceptive use before conception was attempted, number of sexual partners, age at first intercourse, and frequency of intercourse at the time of conception) were not included in the final model because they were judged not to confound the association. When the analysis excluded women who self-referred to the study (n=67), there was little change in the result (FR=0·60, 95% CI 0·45–0·80).

The impaired fecundability in the treated group was seen in those treated with DES (FR=0·63, 95% CI 0·45–0·88) and in those treated with EE (0·55, 0·41–0·75). Significantly reduced fecundability was seen irrespective of the timing of treatment (before menarche FR=0·56, 95% CI 0·41–0·77, after menarche 0·61, 0·45–0·84) and the duration of treatment (≤18 months FR 0·64, 0·44–0·93; 19–25 months 0·55, 0·38–0·81; ≥26 months 0·59, 0·41–0·83).

Discussion

Although the possibility of adverse reproductive effects of oestrogen treatment for tall stature in girls has been acknowledged for many years,[7,8] we believe ours is the first study to report long-term follow-up of the reproductive experiences of a large cohort of treated girls. Our findings indicate that exposure to high-dose oestrogens in adolescence is associated with impaired fertility in later life. This effect was seen as both a reduced per cycle rate of conception in those who conceived, and as an increase in the risk of experiencing infertility. The availability of infertility treatments is likely to have contributed to the finding that women who were treated for tall stature had only a small decrease in the probability of eventually conceiving and having a live birth compared with untreated women. Although this notion provides some reassurance about fertility potential after treatment for tall stature, infertility treatment involves health risks and the financial and emotional costs are substantial for many women.

Although women from both groups were similar in many respects, including socioeconomic status and sexual history, there might have been subtle differences between the groups that were not accounted for in this study. For example, family attitudes to tall stature could have been different between the two groups but there is no reason to expect that such attitudes would be associated with later fertility. Although untreated tall girls were more likely to have a predicted adult height of less than 177 cm and to have little further growth potential at the time of initial assessment, height was not associated with fertility in this cohort, and predicted adult height did not explain the impaired fertility in women who were treated for tall stature. The results of the sensitivity analysis suggest that selective participation in either group was unlikely to have explained the observed effect on fertility.

Measurement of outcomes in this retrospective cohort study relied on self-reported fertility problems and time-to pregnancy for first pregnancies. Although infertility investigations and diagnoses were not verified with medical records, these are salient events for women with fertility problems, and participants were able to recall specific investigations that had been undertaken. Investigations of this type are not usually initiated unless a patient meets clinical criteria for subfertility.

Puberty is a time of maturation of the female reproductive tract and of change in the hypothalamic-pituitary axis. Although it is plausible for supraphysiological doses of oestrogen in adolescence to have long-term effects, the mechanisms involved in reducing reproductive potential are uncertain.

Our results have important implications. For women who had oestrogen treatment for tall stature, it is reassuring that the likelihood of eventually conceiving and having a live birth was only slightly lower than that for untreated women, though treated women took longer to conceive and more required fertility services. Our findings also have implications for our understanding of reproductive biology. The suggestion that oestrogen exposure during puberty might programme reproductive potential in later life opens new opportunities for understanding female infertility.

Contributors

All authors contributed to the design and interpretation of the study. F Bruinsma, A Venn, and D Baird were responsible for data analysis.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We thank the women who participated in the study, members of Tall Girls Inc, and the physicians who provided access to their medical records. We also thank members of the study's reference group for their advice, Lyn Watson for statistical advice, Terry Dwyer for helpful discussions about the manuscript, and Michelle Kingston for research assistance.

References

1 Goldzieher M. Treatment of excessive growth in the adolescent female. *J Clin Endocrinol Metab* 1956; **16:** 249–52.

2 Barnard ND, Scialli AR, Bobela S. The current use of estrogens for growth-suppressant therapy in adolescent girls. *J Pediatr Adolesc Gynecol* 2002; **15:** 23–26.

3 Wettenhall HNB. The tall child. In: Brook CSD, ed. Clinical Paediatric Endocrinology. Oxford: Blackwell Scientific, 1981: 134–40.

4 Normann EK, Trygstad O, Larsen S, Dahl-Jorgensen K. Height reduction in 539 tall girls treated with three different dosages of ethinyloestradiol *Arch Dis Child* 1991; **66:** 1275–78.

5 Conte F, Grumbach M. Epidemiological aspects of estrogen use: estrogen use in children and adolescents: a survey. *Pediatrics* 1978; **62:** 1091–97.

6 Waal de W, Torn M, de Muinck Keizer-Schrama S, Aarsen R, Drop S. Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. *Arch Dis Child* 1995; **73:** 311–15.

7 Wettenhall H, Cahill C, Roche A. Tall girls: a survey of 15 years of management and treatment. *J Pediatr* 1975; **86:** 602–10.

8 Crawford J. Treatment of tall girls with estrogen. *Pediatrics* 1978; **62:** 1189–95.

9 Drop S, Waal de W, de Muinck Keizer-Schrama S. Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; **19:** 540–58.

10 Herbst A, Ulfelder H, Poskanzer D. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 1971; **284:** 878–81.

11 Trygstad O. Oestrogen treatment of adolescent tall girls: short term side effects. *Acta Endocrinol Suppl (Copenh)* 1986; **279:** 170–73.

12 Bayley N, Pinneau S. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. *J Pediatr* 1952; **40:** 423.

13 Weinberg C, Baird D, Rowland A. Pitfalls inherent in retrospective time-to-event studies: the example of time to pregnancy. *Stat Med* 1993; **12:** 867–79.

14 Smith A, Rissel C, Richters J, Griulich A, de Visser R. Reproductive experiences and reproductive health among a representative sample of women. *Aust N Z J Public Health* 2003; **27:** 204–09.