Hormonal changes during the first year of oestrogen treatment in constitutionally tall girls

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Abstract
Objective: Oestrogens are used to inhibit growth in girls with constitutionally tall stature. We studied the changes in different hormones that accompany such therapy.
Subjects and methods: In this longitudinal study we examined the levels of total insulin-like growth factor-I (IGF-I), free thyroxine (FT4), thyrotrophin (TSH), testosterone, dehydroepiandrosterone sulphate (DHEA-S), cortisol and prolactin in two groups of girls receiving ethinyloestradiol at a dose of either 0.1 mg daily (group A, \( n = 22 \)) or 0.2 mg daily (group B, \( n = 36 \)). Hormonal measurements were performed at start of therapy and after 3, 6 and 12 months.
Results: In both groups the levels of IGF-I, testosterone and DHEA-S were reduced while the concentrations of cortisol and prolactin were increased. The pituitary–thyroid axis was not significantly affected by this therapy. The girls receiving 0.2 mg ethinyloestradiol daily had lower IGF-I levels after 12 months of therapy and had higher serum prolactin concentrations than the girls treated with 0.1 mg daily. The reduction in predicted height and the advancement in bone age were similar in both groups.
Conclusions: Therapy with pharmacological doses of ethinyloestradiol changes the levels of several hormones including IGF-I, testosterone, DHEA-S, prolactin and cortisol but the role of the respective changes in the inhibition of growth is not clear. The suppression of DHEA-S levels by 40% suggests that the ovaries contribute significantly to the production of this hormone in pubertal girls.

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Introduction
For more than 50 years, high doses of oestrogens, ranging from 0.3 to 1.0 mg daily, have been used to reduce final height in constitutionally tall girls (1–4). Recently, comparative trials have shown that a dose of ethinyloestradiol as low as 0.1 mg/day was equally effective in reducing final height (5–7). Limited data have been published on the hormonal changes that accompany the treatment with the high doses (8, 9), but no such data are available on treatment with lower doses. We therefore measured serum levels of total insulin-like growth factor-I (IGF-I), free thyroxine (FT4), thyrotrophin (TSH), prolactin, testosterone, dehydroepiandrosterone sulphate (DHEA-S) and cortisol in constitutionally tall girls receiving 0.1 or 0.2 mg/day ethinyloestradiol.

Subjects and methods
Fifty-eight constitutionally tall girls were included in this longitudinal study. The diagnosis was based on (a) familial occurrence of tall stature (height of one or both parents >2 s.d. above the mean), (b) height >2 s.d. for age, according to the standards of Tanner et al. (10), (c) predicted height of more than 180 cm and (d) exclusion of endocrine and other disorders that may explain their tall stature. Skeletal age was evaluated by X-ray of the left hand according to the method of Greulich and Pyle (11). Final height was predicted by the method of Bayley and Pinneau (12).

Before the start of therapy, each patient had reached at least a breast development stage III according to Marshall and Tanner (13). Ethinyloestradiol was given every day: the girls who started treatment after 1995 (group A; \( n = 22 \)) received 0.1 mg and those who started before 1995 (group B; \( n = 36 \)) 0.2 mg ethinyloestradiol daily. This treatment was supplemented with medroxyprogesterone acetate at a dose of 10 mg for the first 12 days of each month. Informed consent was obtained from patients and parents.

Blood samples were collected at the start of therapy and at 3, 6 and 12 months of treatment, between 0800 and 1200 h. IGF-I (Biosource Europe, Fleurus, Belgium), FT4 (Amerlex M, Amersham, Cardiff, UK), testosterone (Orion Diagnostica, Espoo, Finland), DHEA-S (Immunotech,
Table 1 Clinical data and predicted height (means ± s.d.) at the start and after 12 months of therapy in constitutionally tall girls receiving 0.1 mg (group A, n = 22) and 0.2 mg (group B, n = 36) of ethinyloestradiol daily.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of therapy</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Chronological age (years)</td>
<td>13.6 ± 1.5</td>
<td>13.2 ± 1.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.5 ± 2.9</td>
<td>177.7 ± 2.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.8 ± 10.0</td>
<td>63.1 ± 9.3</td>
</tr>
<tr>
<td>Skeletal age (years)</td>
<td>12.8 ± 0.8</td>
<td>14.4 ± 0.8</td>
</tr>
<tr>
<td>Predicted height (cm)</td>
<td>184.0 ± 2.7</td>
<td>180.8 ± 3.0</td>
</tr>
</tbody>
</table>

Marseilles, France), cortisol (DiaSorin, Stillwater, MN, USA) were assayed by radioimmunoassay. Prolactin and TSH (Wallac Delfia, Turku, Finland) were measured by a fluoroenzyme immunoassay. For all the determinations the inter-assay and intra-assay variation was less than 5%, except for IGF-I where it was less than 10%. The levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured to assess compliance and remained below the detection level. In addition, changes in total cholesterol were measured and antithrombin III activity was determined to assess the risk for thromboembolic complications. For each parameter, patients were only included in the analysis if data were available for all four time points.

The results were analysed using the Statistical Package for Social Sciences (SPSS). The auxological data were analysed by t-test. Hormonal data within the groups at different time points were compared using Bonferroni test. The results between both groups at a particular time point were compared by the Mann–Whitney U test. A P value <0.05 was considered significant.

Results

The clinical data including chronological age, height, weight, skeletal age and height prediction at the start and after 12 months of therapy were comparable in both groups (Table 1). After 12 months of treatment, the predicted height was significantly diminished (P < 0.001) in both groups.

The differences between the concentrations of the hormones at the start and after 3, 6 and 12 months of therapy are summarized in Table 2. In addition, the

Table 2 Hormonal changes (means ± s.d.) in constitutionally tall girls treated with ethinyloestradiol. The table shows the absolute values at the start and the difference (positive or negative) after 3, 6 and 12 months of therapy. For each parameter, patients were only included when data were available for all four time points (a: P < 0.05 for differences between the groups at a given time point; Mann–Whitney U test).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of cases</th>
<th>Values at start</th>
<th>Δ values after 3 months</th>
<th>Δ values after 6 months</th>
<th>Δ values after 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (ng/ml)</td>
<td>0.1 mg daily</td>
<td>14</td>
<td>413 ± 129</td>
<td>−66 ± 123</td>
<td>−98 ± 108</td>
</tr>
<tr>
<td></td>
<td>0.2 mg daily</td>
<td>17</td>
<td>478 ± 110</td>
<td>−130 ± 114</td>
<td>−164 ± 110</td>
</tr>
<tr>
<td>FT₄ (pmol/l)</td>
<td>0.1 mg daily</td>
<td>9</td>
<td>13.53 ± 1.50</td>
<td>−0.03 ± 2.74</td>
<td>−0.10 ± 2.17</td>
</tr>
<tr>
<td></td>
<td>0.2 mg daily</td>
<td>21</td>
<td>14.12 ± 1.87</td>
<td>−0.32 ± 2.03</td>
<td>−0.70 ± 2.45</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>0.1 mg daily</td>
<td>8</td>
<td>1.60 ± 0.60</td>
<td>−0.16 ± 0.45</td>
<td>0.35 ± 1.00</td>
</tr>
<tr>
<td></td>
<td>0.2 mg daily</td>
<td>17</td>
<td>1.50 ± 0.50</td>
<td>0.26 ± 0.52</td>
<td>0.44 ± 0.99</td>
</tr>
<tr>
<td>Prolactin (µU/ml)</td>
<td>0.1 mg daily</td>
<td>15</td>
<td>183 ± 50</td>
<td>229 ± 213^a</td>
<td>136 ± 112^a</td>
</tr>
<tr>
<td></td>
<td>0.2 mg daily</td>
<td>20</td>
<td>198 ± 86</td>
<td>375 ± 252^a</td>
<td>226 ± 132^a</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>0.1 mg daily</td>
<td>7</td>
<td>0.55 ± 0.26</td>
<td>−0.07 ± 0.35</td>
<td>−0.18 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>0.2 mg daily</td>
<td>14</td>
<td>0.55 ± 0.38</td>
<td>−0.21 ± 0.35</td>
<td>−0.23 ± 0.36</td>
</tr>
<tr>
<td>DHEA-S (ng/ml)</td>
<td>0.1 mg daily</td>
<td>14</td>
<td>752 ± 296</td>
<td>−334 ± 198</td>
<td>−369 ± 227</td>
</tr>
<tr>
<td></td>
<td>0.2 mg daily</td>
<td>20</td>
<td>765 ± 434</td>
<td>−305 ± 267</td>
<td>−348 ± 258</td>
</tr>
<tr>
<td>Cortisol (ng/ml)</td>
<td>0.1 mg daily</td>
<td>14</td>
<td>93 ± 50</td>
<td>216 ± 87</td>
<td>270 ± 66</td>
</tr>
<tr>
<td></td>
<td>0.2 mg daily</td>
<td>19</td>
<td>99 ± 45</td>
<td>229 ± 133</td>
<td>274 ± 132</td>
</tr>
</tbody>
</table>
absolute values of some selected parameters are represented in Figs 1–3.

Figure 1 shows the levels of total IGF-I before and after 3, 6 and 12 months of therapy. In both groups, IGF-I concentrations were significantly suppressed after 3 months of treatment. In group A, IGF-I levels remained at that level up to 12 months, whereas in the girls receiving 0.2 mg total IGF-I further decreased at 6 and 12 months of therapy. At all time points, the suppression of IGF-I was more accentuated in group B than in group A and reached statistical significance after a treatment period of 12 months.

FT₄ and TSH values were barely influenced by oestrogen therapy (Table 2) and remained within the normal range in the two groups. In group B, FT₄ continued to decline during the first year. In both groups, the changes in TSH concentration inversely correlated with the FT₄ levels, increasing temporarily at 6 months of therapy.

A marked increase in prolactin concentration occurred in both groups with maximal levels after 3 months of therapy (Fig. 2). The stimulation of prolactin secretion by oestrogens was more pronounced in group B at each time point.

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The levels of DHEA-S decreased significantly (P < 0.05) by about 40% after 3 months of treatment and remained suppressed for at least 12 months, irrespective of the dose used. Testosterone concentrations were also clearly influenced by oestrogen therapy and decreased about 40% (P < 0.05) after 6 months (Fig. 3).

Serum cortisol levels increased 3-fold in both groups during the whole study period (Table 2).
During oestrogen therapy, serum cholesterol levels rose 25% in both groups. After 12 months of therapy, the antithrombin III activity was unaffected in group A but significantly decreased by 12% in group B (P < 0.05).

Discussion

In this study we have measured the influence of two pharmacological doses of oestrogens on the plasma levels of various hormones in constitutionally tall girls. Treatment with ethinylestradiol at doses of 0.1 and 0.2 mg daily resulted in an effective growth inhibition, thus confirming earlier reports (5–7). Whether even lower doses are equally effective on the growth process remains to be assessed.

Our results show that the administration of 0.1 or 0.2 mg ethinylestradiol is accompanied by important changes in the serum levels of various hormones: a suppression of total IGF-I, DHEA-S and testosterone and an increase of prolactin and cortisol. FT₄ and TSH levels did not change significantly.

In children and adolescents the effect of ethinylestradiol on growth appears to depend on the dose (14). Physiological doses up to 0.03 mg daily stimulated growth rate and increased serum IGF-I levels during spontaneous (15) and induced (16) puberty. Pharmacological doses of 0.25 mg and higher, however, resulted in growth inhibition and a decrease in serum IGF-I levels both in constitutionally tall girls (2, 8, 17) and in acromegalic patients (18). Our data indicate that this is also the case when doses of 0.1 and 0.2 mg are used.

The effect of oestrogens on serum IGF-I, however, not only depends on the dose but also on the age of the patient. Whereas physiological doses of oestrogens increase IGF-I levels in young girls, similar doses suppress IGF-I when given as contraceptives in young adult females (19) or as oral replacement therapy in postmenopausal women (20–22). A similar age-dependent effect of oestrogens on IGF-I was recently reported in primates at all ages (23).

The increase of total IGF-I in adolescent girls by physiological doses of oestrogens is caused by an increase in growth hormone (GH) secretion (24). Surprisingly, the suppression of IGF-I observed in adults with similar doses is also accompanied by an enhanced GH secretion (20, 21). Weissberger et al. therefore speculated that oral oestrogen administration inhibits liver IGF-I production (20). These authors demonstrated that IGF-I levels were not suppressed in postmenopausal women with transdermal oestrogen replacement therapy, in whom the liver was not exposed to high concentrations of oestrogens as opposed to oral replacement. In addition, studies in animals confirmed the inhibitory effect of oestrogens on hepatic mRNA synthesis for IGF-I (25).

A decrease in serum IGF-I may also be the result of a reduction in serum IGF binding proteins (IGFBPs). However, IGFBP-3, which is the main IGFBP present in serum, was not altered by oestrogen replacement therapy in postmenopausal women (20, 21) and was even increased by similar doses in primates at all ages (23).

The alterations in the pituitary–thyroid axis that we observed were small and therefore may not be of any physiological significance. Indeed, FT₄ concentrations did not change during ethinylestradiol treatment with 0.1 mg and barely decreased in the girls receiving 0.2 mg. These results are in agreement with those of other studies (26).

In our study population, the treatment with high doses of ethinylestradiol reduced circulating DHEA-S levels by about 40%. Accordingly, ethinylestradiol in contraceptive doses also reduced DHEA-S levels by 20–40% (27, 28). However, oestrogen replacement failed to change DHEA-S levels in subjects with impaired ovarian function such as Turner patients (9) or postmenopausal women (20, 29). These findings strongly suggest that the ovaries contribute substantially to the serum DHEA-S levels and contradict the generally accepted view that only about 5–10% of circulating DHEA-S is of ovarian origin. Moreover, there is no convincing evidence indicating that oestrogens can inhibit adrenal androgen synthesis (9). The decline in serum testosterone that we observed during oestrogen therapy may also be the result of inhibition of ovarian function, since both ovaries and adrenals equally contribute to testosterone production in females.

The rise in cortisol concentration most probably resulted from an increase in transcortin levels. This effect on cortisol has been well documented with high and low oestrogen doses and has been shown to be reversible once the treatment is arrested (9, 27).

Our observation that oestrogens increase prolactin levels has been previously reported (30, 31). Oestrogens transiently enhanced prolactin release both in vitro (32, 33) and in vivo (34, 35). Trygstad (36) observed galactorrhoea and high prolactin levels in 16 out of 680 girls treated with high doses of oestrogens. In our population, no hyperprolactinaemia nor galactorrhoea was found. Since the oestrogen-induced prolactin release was shown to be antagonized by medroxyprogesterone acetate (37), it is indicated to add sufficient amounts of progesterone derivatives to the therapy.

It is unclear to what extent these hormonal changes contribute to the growth-inhibiting effect of pharmacological doses of oestrogens. One of the striking effects of oestrogen treatment in our patients was the acceleration of skeletal maturation, which was also observed by other authors (9). Bone age advanced by 20 months in group A and by 22 months in group B after 12 months of therapy. Bone age maturation is known to be accelerated by IGF-I, thyroxine and androgens, but all these hormones were suppressed by oestrogen.
therapy. Other mechanisms must therefore be involved, including a local effect of oestrogens on the growth plate, e.g. by the modulation of the paracrine and autocrine functions of IGF-I (38).

To conclude, our data indicate that 0.1 and 0.2 mg ethinylestrodiol are equipotent with respect to growth inhibition and the promotion of skeletal maturation. The high dose however caused a significantly higher increase in prolactin concentrations and decreased antithrombin activity. We therefore suggest, for safety reasons, abandoning the use of 0.2 mg ethinylestrodiol to inhibit longitudinal growth in girls with constitutional tall stature.

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References


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