Influence of oestrogen in high and low doses on plasma steroid concentrations in girls with tall stature and Turner syndrome

M. Zachmann, B. Manella, U. Eiholzer, H. Bucher and A. Prader

Department of Paediatrics, University of Zürich, Kinderspital, 8032 Zürich, Switzerland

Abstract. Plasma DHA, 17-OH-progesterone, androstenedione, testosterone, cortisol, oestrone and oestradiol were determined before and on high dose oestrogen treatment (1, 3, 6 and 16 months) given to excessively tall girls to reduce future adult height. Basal values were normal: DHA 16.4 ± 0.8 nmol/l (n = 90), 17-OH-progesterone 4.9 ± 0.3 (n = 20), androstenedione 5.6 ± 0.3 (n = 25), testosterone 2.6 ± 0.3 (n = 24) and cortisol 395 ± 20 (n = 90). On treatment, DHA, 17-OH-progesterone and androstenedione decreased to a minimum of 9.3 ± 1.0 nmol/l (3 months, n = 13), 2.4 ± 0.3 (6 months, n = 7) and 2.6 ± 0.2 (6 months, n = 9), respectively, while testosterone remained unchanged, and cortisol increased to a maximum of 825 ± 99 nmol/l (16 months, n = 23). In 15 girls with XO gonadal dysgenesis, basal DHA was low (11.8 ± 1.0 nmol/l), and did not significantly change on low dose oestrogen replacement (13.3 ± 1.4). The cause of the fall in plasma concentrations of androstenedione, DHA and 17-OH-progesterone in treated tall girls is unknown, but it is speculated that it might be related to peripheral conversion in the augmented adipose tissue mass. The rise in plasma cortisol, on the other hand, is probably due to increased transcortin.

Clinical experience seems to indicate that oestrogens are capable of stimulating adrenal androgen secretion in girls. This belief has been expressed in older textbook, Wilkins (1962) states: 'In fact, oestrogens may cause increased androgen production as demonstrated by the fact that when patients with the 'syndrome of gonadal aplasia' are treated with oestrogens there is increase in the pubic hair and 17-ketosteroid output'.

Since then, somewhat contradictory observations have been made concerning the effect of oestrogens on adrenal androgen secretion. While in vitro, oestrogens seem to have an inhibitory effect on 3β-hydroxysteroid dehydrogenase activity in human adrenal tissue (Yanaihara & Troen 1972; Yates & Desphande 1974) and thus appear to be capable of increasing DHA production at the expense of Δ4-steroids, most recent in vivo studies fail to demonstrate a stimulating, but rather suggest a reducing effect on androgen secretion (Madden et al. 1978; Fern et al. 1978; for discussion see Sklar et al. 1981).

The effects of oestrogens on androgen levels might be different depending on origin (endogenous or exogenous), quantity (replacement, oral contraception, or treatment of tall stature), and time of exposure. For this reason, we decided to follow DHA and some other steroids in tall girls on high dose oestrogen treatment, and to compare the results with some limited data in girls with XO gonadal dysgenesis on low dose replacement therapy.

Patients and Methods

Excessively tall girls treated with high doses of oestrogens to reduce adult stature, and girls with Turner syndrome on oestrogen replacement were studied.

Mean chronologic age of 23 tall girls at the start of
treatment was 13.3 ± 1.4 years (range 11.2 to 14.6 years), and mean bone age 13.1 ± 0.6 years (Greulich & Pyle 1959). All had familial tall stature, and were considered as normal subjects. Girls suffering from pathologic types of tall stature were excluded.

Treatment consisted of ethinyl oestradiol 0.3 mg daily by mouth continuously, and norethisterone, 10 mg daily for 6 days every fourth week in 9 girls, and of oestradiol valerate 40 mg im every 2 weeks with the same norethisterone schedule in 14 girls. Mean duration of treatment was 1.4 ± 0.4 years.

The 15 girls with Turner syndrome had either XO sex chromosome constitution, or a ring chromosome, but none had a XO/XX-mosaicism with spontaneous puberty. Their mean chronologic age at initiation of replacement was 16.3 ± 2.2 years (range 13.5 to 17.2), their mean bone age 12.2 ± 0.6 years. Replacement consisted of oral ethinyl oestradiol 0.01 mg daily for 3 weeks, followed by a 1 week interval.

While estimations of DHEA and cortisol were carried out routinely in 90 girls before treatment as part of a pre-treatment evaluation programme, and their results are included in the basal values, repeated longitudinal determinations during and after treatment and estimation of 17-OH-progesterone, androstenedione, testosterone, oestrone and oestradiol were performed in the 23 or fewer girls only.

Blood samples were obtained during the second week (day 7 to 13) of the cycle as frequently as possible, and as closely as possible to 1, 3 and 6 months of treatment in the tall girls, and around 6 months of treatment in the girls with Turner syndrome. Plasma steroids were determined as previously described (Zachmann & Prader 1978; Zachmann et al. 1979). For statistical analysis, standard procedures (Student’s t-test, paired t-test) were used.

Results

a) Tall girls

The results are shown in Figs. 1 and 2, and in Table 1.

Before treatment, all steroids were within normal limits, with values of DHA of 16.4 ± 0.8 (SEM, n = 90), 17-OH-progesterone 4.9 ± 0.3 (n = 20), androstenedione 5.6 ± 0.3 (n = 25), testosterone
During treatment, the plasma levels of DHA, 17-OH-progesterone and androstenedione did decrease significantly (Fig. 1): DHA to a minimum of 9.3 nmol/l after 3 months (n = 23, P < 0.001), 17-OH-progesterone to 2.4 nmol/l (n = 15, P < 0.001), and androstenedione to 2.6 nmol/l (n = 23, P < 0.001), both after 6 months of treatment. By contrast, testosterone levels, although generally lower on treatment (1.9 ± 0.4 to 2.4 ± 0.4 nmol/l, n = 14), were not significantly different from the basal values.

In contrast to the mentioned steroids, which did either decrease or remained unchanged, cortisol levels increased markedly during treatment to 554 ± 40 nmol/l (n = 13, P < 0.01) after 3 months and 825 ± 99 nmol/l (n = 23, P < 0.001) after 16 months (Fig. 2). After 16 months of treatment, there was an escape phenomenon for the DHA-levels, which increased to 13.7 ± 0.9 nmol/l (n = 23). The same trend seemed to exist for 17-OH-progesterone and androstenedione, but the number of estimations is too low to draw any conclusions. The values of the girls on oral treatment were at no time significantly different from the values of the girls on im treatment. Also the basal values of the 23 longitudinally studied girls were not significantly different from those in the 67 girls, whose basal values only are available. Therefore, the combined results are presented.

Only limited results from 9 girls are available concerning oestrogen levels (Table 1). Because 3 patients were receiving oral ethinyl oestradiol, and 6 im oestradiol valerate, and because the radio-immunoassay is specific for oestrone and oestradiol, and – with column chromatography – does not cross-react with ethinyl oestradiol, the results from these two small subgroups could not be combined.

In the orally treated patients, oestrone increased, and oestradiol decreased slightly, but both changes were not significant, and the number of estimations is small.

After treatment, DHA increased considerably (21.3 ± 1.9 nmol/l, n = 22, 3.5 months after discontinuation), and became even significantly higher than

\[
2.6 \pm 0.3 \text{ (n = 24), cortisol } 395 \pm 20 \text{ nmol/l (n = 90), oestrone } 578 \pm 72 \text{ (n = 9) and oestradiol } 534 \pm 107 \text{ pmol/l (n = 9).}
\]

Fig. 2.

Changes of plasma cortisol in tall girls treated with high doses of oestrogens.

\[
\text{nmol/l} \quad 800 \quad 700 \quad 600 \quad 500 \quad 400 \quad 300
\]

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>16</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>on treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>off treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Downloaded from Bioscientifica.com at 10/15/2018 09:34:34PM via free access
before treatment ($P < 0.01$). Cortisol returned to normal ($494 \pm 49$ nmol/l, $n = 22$), but was still slightly significantly above basal values ($P < 0.05$).

Unfortunately, values of 17-OH-progesterone, androstenedione and testosterone are not available after discontinuation. Both oestrogens were weakly significantly higher ($P < 0.05$) 2.7 months after discontinuation, than before treatment.

b) Girls with Turner syndrome
In the 15 girls with Turner syndrome, DHA was low ($11.8 \pm 1.03$ nmol/l) even for bone age and did not significantly change after 6.9 months of low dose oestrogen replacement therapy ($13.3 \pm 1.42$ nmol/l).

Discussion
Our results confirm our preliminary ones with a smaller number of cases (Bucher et al. 1981), and show that high doses of oestrogens given to tall, normal girls in puberty reduce the plasma levels of adrenal androgens as represented by DHA and androstenedione, as well as 17-OH-progesterone, leave testosterone unchanged, and increase cortisol and probably also oestrone. In contrast, DHA remains low and unchanged on low-dose oestrogen replacement in girls with Turner syndrome. The androgen reduction is probably of biological relevance, since there is often considerable improvement or disappearance of acne, if it was present before treatment (Zachmann et al. 1975). The other changes do not seem to be of clinical or biological importance. The following factors may play a role in the observed alterations: 1) changes of sex hormone binding globulin and transcortin; 2) changes of steroid secretion rates in the ovaries and/or adrenals secondary to gonadotrophin suppression and/or alteration of ACTH or prolactin secretion; 3) influence on enzymes involved in the steroid biosynthesis; and 4) changes of peripheral steroid conversion; finally 5) the hypothetical 'adrenarche factor' might be suppressed by oestrogens.

Since the observed changes are not homogeneous in time and direction, it is unlikely that only a single one of these factors is involved, and since the samples were taken during days 7 to 13 of the cycle in order to minimize possible effects of the progestin treatment, the effects appear to be exclusively due to the oestrogen treatment.

Table 1.

Plasma oestrogens before, during and after high-dose oestrogen treatment in tall girls (pmol/l)

<table>
<thead>
<tr>
<th></th>
<th>before</th>
<th>on E</th>
<th>during</th>
<th>on V</th>
<th>after</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oestrone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>578</td>
<td>806a</td>
<td>2539b**</td>
<td>1339*</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>72</td>
<td>156</td>
<td>537</td>
<td>436</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Oestradiol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>534</td>
<td>407a</td>
<td>34749b**</td>
<td>1761*</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>107</td>
<td>152</td>
<td>642</td>
<td>656</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

E: ethinyl oestradiol, V: oestradiol valerate.
Mean duration of treatment: a: 6.0 ± 2.4 months; b: 1.9 ± 0.6 months.
Values after treatment: 2.7 ± 1.6 months after discontinuation.
Significance of difference to basal value: * $P < 0.05$. ** $P < 0.001$. 

Explanation is easiest for the increased cortisol levels, since oestrogens and progesterone increase transcortin (Hartmann et al. 1981).

The reductions of androstenedione, DHA and 17-OH-progesterone are more difficult to explain. Sex hormone binding globulin, which increases on high oestrogen doses, cannot explain the drop in androstenedione and DHA, and 17-OH-progesterone, which is bound to transcortin would tend to increase as cortisol (Dunn et al. 1981). The slightly lower levels of plasma DHA, androstenedione, pregnenolone and 17-OH-pregnenolone in women taking oral contraceptives have been attributed to reduced adrenal secretion of DHA-sulphate, suppression of ACTH (Madden et al. 1978), or oestrogen- and/or gestagen-induced inhibition of pregnenolone formation from cholesterol (Fern et al. 1978).

The gonadotrophins are suppressed in treated tall girls, but since only small quantities of androstenedione and DHA are formed in the ovaries, this suppression cannot explain our findings. Prolactin, which increased considerably on treatment (Bucher et al. 1981), can also not be responsible for the drop, because in women with hyperprolactinaemia, galactorrhoea, and amenorrhoea, adrenal androgens are higher than in normal women (Lobo et al. 1980).

DHA normally increases during adrenarche (Schiebinger et al. 1981). This is due to a rise of the 17-hydroxylase and 17,20-desmolase activities. In our patients, inhibition of 17-hydroxylase activity is unlikely, because cortisol did not decrease. Inhibition of 17,20-desmolase activity can be excluded, because DHA and androstenedione were not relatively lower than 17-OH-progesterone (Zachmann et al. 1982). Involvement of the 3β-hydroxysteroid dehydrogenase can be excluded by the quantitatively similar course of DHA and androstenedione.

Peripheral aromatization of androstenedione to oestrone and oestradiol is known to occur in liver (Frost et al. 1980), breast (Perel et al. 1980), and adipose tissue (Forney et al. 1981). It seems to occur regardless of maturational stage, and gonadal function, and has also been observed in obese males (Kley et al. 1980).

In our tall girls, there is considerable weight gain on treatment (Zachmann et al. 1975; Atarés et al., in prep.). If one assumes that about half the gain during the first 6 months is due to increased formation of adipose tissue, the mean addition of fat would correspond to about 3.5 kg, a quantity, which might be sufficient to increase steroid aromatization. The number of oestrogen estimations in patients on oral ethinyl oestradiol is, however, insufficient to support this hypothesis, and the oestrogen levels in the patients treated with oestradiol valerate are not informative in this respect, because they are of exogenous origin.

The results in patients with Turner syndrome are rudimentary. In them, there was only a small weight gain, and DHA did not change. Their basal DHA-levels were lower than in normal girls with comparable bone age, as has been observed by Apter et al. (1982), and there is no evident explanation for this. Our results with respect to replacement-doses are in agreement with those of Sklar et al. (1981).

In conclusion, we have shown that there are consistent plasma steroid changes on high-dose oestrogen treatment, while replacement doses have no such effect. The cause of the reduction of androgen and 17-OH-progesterone levels by high doses of oestrogens is unknown, but it is speculated that peripheral aromatization might at least play a partial role.

Acknowledgments

This work was supported by the Swiss National Science Foundation (Grants No. 3.959-0.80 and 3.874-0.83).

References


Received on January 20th, 1984.