THE FUNCTIONAL STATE OF THE HYPOTHALAMO-PITUITARY AXIS AFTER HIGH-DOSE OESTROGEN THERAPY IN EXCESSIVELY TALL GIRLS

By

J. P. Hanker¹, G. Schellong² and H. P. G. Schneider¹

ABSTRACT

Sixteen excessively tall girls were treated with 0.3 mg of ethinyloestradiol daily and 10 mg of norethisterone for 5 days every 3 weeks for 7–26 months. The reduction of adult height varied from 0–12.3 cm, depending on the bone age (11⁵/₁₂–14⁸/₁₂) before treatment. The more advanced the bone age was the less final adult height was reduced.

The functional state of the hypothalamo-pituitary axis was assessed by standardized LH-RH testing immediately after termination of therapy as well as 1, 4, 8 and 12 weeks thereafter. Basal levels of oestradiol and prolactin were recorded before each test. Absent LH-responses to LH-RH were observed in all girls when therapy was stopped. Four to eight weeks later the LH responses had normalized in 13 girls and 12 weeks after therapy normal LH responses were found in 14 girls.

Mean basal oestradiol levels were low (20 ± 9 pg/ml) (X ± sd) at the end of therapy but increased significantly (P < 0.0025) to levels similar to different stages of the menstrual cycle after 4 weeks. In contrast mean basal prolactin levels were elevated (21 ± 9 ng/ml) (X ± sn) when therapy was stopped. Within one week a significant (P < 0.01) decrease to values averaging 13 ± 4 ng/ml (sn) was seen. A further but only moderate decline occurred until the 12th week after therapy. The decrease of prolactin paralleled the same extent the increase of endogenous oestradiol. All girls experienced spontaneous menstrual bleedings within 3 to 22 weeks after termination of therapy. In all cases but one menstruation has been regular since.

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The data presented suggest that no major functional disturbance of the hypothalamo-pituitary axis has to be expected after long-term steroid treatment in excessively tall girls.

From clinical observations in precocious puberty it is well known that gonadal steroids reduce adult height by an acceleration of bone maturation and rapid epiphyseal closure. These findings initiated the idea to administer pharmacological doses of sex steroids to girls in whom an excessive tall stature is predicted. Since the early reports by Goldzieher (1956) and until present numerous publications have appeared in the literature (Baley et al. 1962; Whitelaw & Foster 1962; Wettenhall & Roche 1965; Greenblatt et al. 1966; Whitelaw 1967; Frasier & Smith 1968; Schoen et al. 1973; Wettenhall et al. 1975; Zachmann et al. 1975) demonstrating the effectiveness of these steroids to reduce adult height. Different therapeutical regimens as well as different methods used for height predictions (Bailey & Pinneau 1952; Greulich & Pyle 1950; Tanner et al. 1966) make it difficult to compare the results. Moreover, there is still no consent about the lower limit of predicted final height above which hormonal treatment should be started. It is, however, generally accepted that the reduction of adult height is greatest when a hormonal intervention is started as early as possible, preferably before the pubertal growth spurt occurs; at least before menarche. Under these conditions the actual menarche is exogenously and prematurely induced. We were interested in the functional state of the hypothalamo-pituitary axis (gonadostat) in excessively tall girls after long-term and high-dose steroid therapy which was started when the normal regulatory function of the gonadostat was not yet fully established.

MATERIAL AND METHODS

Sixteen girls who were referred either to the children's clinic or women's hospital because of an idiopathic excessive tall stature underwent hormonal treatment for a mean duration of 20.1 ± 5.9 (X ± sd) months (range: 7–26 months). Written informed consent was obtained from all parents.

Following the regimen published by Zachmann et al. (1975) ethinyloestradiol (= EOe) was given continuously as an oral dose of 0.3 mg/day. Every 3 weeks 10 mg of nortestosterone was added for 5 days. Thus, regular withdrawal bleedings occurred. Table 1 summarizes chronological age, bone age, weight, and actual height of the girls before as well as after therapy. For bone age estimation X-rays of the left hand and wrist were taken before therapy, at 1/2 year intervals during therapy and after termination of it. The X-rays were rated following the TW 2 system (Tanner et al. 1975b). Adult height was predicted according to the method of Tanner et al. (1975a) which takes into account actual height, bone age, occurrence of menarche, and midparent height. In our girls predictions of the final height differed from 178.2 to 193.2 cm, averaging 184.0 ± 4.0 cm (sd) before therapy. At the end of the hormonal treatment predictions varied from 174.1 to 190.9 cm, now averaging 180.0 ± 4.0 cm (sd) (Table 1).
In general therapy was started when the lower limit of adult height prediction was 180 cm. In two cases (K.B. and G.M.) it was started despite adult height predictions of 178.2 and 179.8 cm, respectively, because for psychological reasons. In all girls thelarche and pubarche had occurred, whereas, only one girl (G.M.) had experienced menarche before onset of treatment.

Therapy was stopped at a skeletal age of 14½±15½ years. For the endocrine follow-up in all girls defined LH-RH tests (Keller et al. 1973) were performed immediately after termination of therapy, as well as after 1, 4, 8 and 12 weeks. The LH responses to a 25 ng bolus of LH-RH were classified as normal (=R₂), impaired (=R₁), or absent (=R₀) by both the absolute and net increases of circulating LH, as recorded 25 min after the LH-RH injection. LH was measured by means of RIA (Midgley 1966), and is expressed as ng/ml LER 907.

Before each LH-RH test basal values of prolactin (PRL) and oestradiol (Oe₂) were recorded. Both hormones were measured radioimmunologically (Franchimont et al. 1976). Prolactin levels are expressed as ng/ml NIH, those for Oe₂ as pg/ml MRC. For statistical evaluation of our data the paired Student’s t-test was used.

**RESULTS**

Table 1 summarizes height predictions in all girls before and after therapy. On average adult height was significantly (P < 0.005) reduced by 4.03 ± 3.20 (SD) cm (range: 0–12.3 cm).

This reduction was greatest in the biologically youngest group. The more the biological age had advanced the less adult height was reduced (Table 2).

The LH responses to LH-RH are illustrated in Fig. 1; the corresponding net increases in Fig. 2.

In all girls who had undergone LH-RH testing immediately after termination of therapy an absent LH response (=R₀) was observed (Table 3). This is evidenced by both, the absolute LH levels (Fig. 1), and the net increases (Fig. 2).

One week after therapy a normal LH response (=R₂) was found in one girl (F.B.), whereas, in 13 girls it still was absent (Figs. 1 and 2, Table 3). Four weeks after discontinuation of the treatment normal responses (=R₂) were recorded in 9 girls, impaired responses (=R₁) in 2, and absent responses (=R₀) in 4. After another 4 weeks all impaired responses had normalized, whereas, in 2 girls (H.A. and M.B.) the responses still were absent.

Twelve weeks after therapy had been withdrawn, 2 girls (H.A. and B.G.) still did not respond to LH-RH. At this time 13 girls exhibited a normal LH response. In one girl (G.M.) an impaired response was now recorded; however, in her case a normal response was found 4 weeks previously (Table 3).

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1) For this endocrine follow-up again written informed consent was obtained from all parents.
**Table 1.**
Hormonal therapy in 16 girls presenting with an excessive tall stature.

<table>
<thead>
<tr>
<th></th>
<th>Before therapy</th>
<th>After therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronological age, years</strong></td>
<td>127/12 ± 1/12</td>
<td>143/12 ± 1/12</td>
</tr>
<tr>
<td><em>(mean ± sd)</em></td>
<td>(10-15/12)</td>
<td>(12-16/12)</td>
</tr>
<tr>
<td><strong>Bone age, years</strong></td>
<td>13/12 ± 1</td>
<td>15/12 ± 1</td>
</tr>
<tr>
<td><em>(11-14/12)</em></td>
<td><em>(14-16)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>175.2 ± 5.4</td>
<td>177.8 ± 4.4</td>
</tr>
<tr>
<td><em>(166.5-188)</em></td>
<td><em>(171.3-190)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Expected final height, cm</strong></td>
<td>184.0 ± 4.0</td>
<td>180.0 ± 4.0</td>
</tr>
<tr>
<td><em>(178.2-193.2)</em></td>
<td><em>(174.1-190.9)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>55.5 ± 8.2</td>
<td>62.4 ± 7.8</td>
</tr>
<tr>
<td><em>(42.5-76)</em></td>
<td><em>(47-76.5)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of therapy, months</strong></td>
<td>20.1 ± 5.9</td>
<td><em>(7-26)</em></td>
</tr>
<tr>
<td><em>(mean ± sd)</em></td>
<td></td>
<td></td>
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<tr>
<td><strong>Reduction of expected final height, cm</strong></td>
<td>4.03 ± 3.20</td>
<td><em>(0-12.30)</em></td>
</tr>
</tbody>
</table>

**Table 2.**
Reduction of adult height depending on bone age recorded before therapy.

<table>
<thead>
<tr>
<th>Bone age (years)</th>
<th>N</th>
<th>Height prediction</th>
<th></th>
<th>Reduction (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before therapy</td>
<td>After therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(cm)</td>
<td>(cm)</td>
<td></td>
</tr>
<tr>
<td>11–11 1/2</td>
<td>1</td>
<td>186.40</td>
<td>174.10</td>
<td>12.3</td>
</tr>
<tr>
<td>12–12 1/12</td>
<td>5</td>
<td>184.96</td>
<td>179.56</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>180.3–189.7</td>
<td>176.0–183.5</td>
<td>3.5–9.4</td>
</tr>
<tr>
<td>13–13 1/12</td>
<td>4</td>
<td>183.13</td>
<td>178.98</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>178.2–185.7</td>
<td>178.7–181.7</td>
<td>2.6–5.6</td>
</tr>
<tr>
<td>14–14 1/12</td>
<td>6</td>
<td>183.45</td>
<td>182.10</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>179.8–193.2</td>
<td>179.6–190.9</td>
<td>0–2.8</td>
</tr>
</tbody>
</table>
**Fig. 1.**
LH responses to LH-RH after termination of therapy.

**Fig. 2.**
Net increases of LH as recorded 25 min after a 25 µg bolus of LH-RH.
In all girls spontaneous menstrual bleedings occurred. The onset varied between 5 and 22 weeks, averaging 6.8 ± 5.1 (sd) weeks after termination of therapy. In all cases but one (S. M.) menses were regular (Table 3).

Mean basal oestradiol levels were 20 ± 9 pg/ml (sd) at the end of therapy, and 24 ± 19 pg/ml (sd) one week later. After another 4 weeks they had significantly ($P < 0.0025$) increased to 119 ± 74 pg/ml (sd). No further rise was observed after 8 and 12 weeks, the figures being 96 ± 56 and 128 ± 106 pg/ml (sd), respectively. The range of the basal levels recorded 4, 8 and 12 weeks after therapy was similar to oestradiol levels found at different stages of the menstrual cycle (Fig. 3).

Mean basal prolactin levels were 21 ± 9 ng/ml (sd) right after termination.
of therapy. Within one week a significant ($P < 0.01$) decrease to values of $13 \pm 4$ ng/ml (sd) occurred. A further but only moderate decline was seen after 4, 8 and 12 weeks. The figures were $12 \pm 5$, $10 \pm 4$ and $9 \pm 4$ ng/ml, respectively (all values $\bar{X} \pm sd$) (Fig. 4).

**DISCUSSION**

It is well established that pharmacological doses of sex steroids reduce adult height in excessively tall girls. The extent of this reduction mainly depends on the biological age of the girls at which these hormones are administered (Greenblatt et al. 1966; Whitelaw 1967).

In consent with these data we observed that adult height was reduced most in those girls, whose bone age varied from 11 to 13 years. With advancing biological age the reduction declined impressively.

![Fig. 3. Basal oestradiol-17β levels as recorded immediately after termination of therapy as well as after 1, 4, 8 and 12 weeks.](image-url)
No reports exist in the literature about the functional state of the hypothalamic-pituitary unit after long-term steroid treatment in excessively tall girls. In the assessment of the functional state of the gonadostat the LH-RH test is of particular value. So it could be demonstrated that different functional states are evolved during pubertal development (Job et al. 1972; Franchimont et al. 1974; Garnier et al. 1974; Reiter et al. 1976; Dickermann et al. 1976), or the menstrual cycle (Nillius & Wide 1972; Yen et al. 1972). In different diseases the functional states may be the same as under certain physiological conditions. Moreover, one disease can evolve through different states with time (Franchimont et al. 1975; Sagel et al. 1975; Nillius & Wide 1975; Bohnet et al. 1976). For evaluation of the LH-RH test the LH response to LH-RH proved
to be the most consistent parameter. Thus characteristic LH responses could be related to different stages of puberty, whereas, the FSH responses did not exhibit such changes (Franchimont et al. 1974). Furthermore, in functional disorders of the hypothalamic axis a decrease of the LH response appears much earlier than a decrease of the FSH response (Keller et al. 1976; Zarate et al. 1974). We, therefore, used the LH responses to a standardized test-dose for classification into normal (= R₂), impaired (= R₁), or absent (= R₀) responses (Keller et al. 1975).

In all girls tested immediately after termination of therapy the LH responses to LH-RH were absent. Similar responses are typical for a pre-pubertal stage (Franchimont et al. 1974). Within 4–8 weeks to follow most of our patients developed normal responses, now similar to an adult state (Franchimont et al. 1974; Nillius & Wide 1972). The gonadostat had thus rapidly and spontaneously undergone functional changes as observed during normal pubertal development.

It is well established that oestrogens exert both a negative and positive feedback at the pituitary and hypothalamic level (Thompson et al. 1973; Yen et al. 1974; Keye & Jaffe 1975; Lasley et al. 1975). Due to the negative feedback, exerted by EOE, the LH responses to LH-RH were absent in all girls immediately after therapy was terminated. After withdrawal of the exogenous steroids, endogenous oestradiol rose progressively to levels as recorded at different stages of the menstrual cycle. In parallel in most girls pituitary sensitivity increased to normal. These observations are in consent with data obtained by other investigators demonstrating that pituitary LH content and release are regulated by both, LH-RH and oestradiol (Lasley et al. 1975; Wang et al. 1976). In contrast the LH responses to LH-RH remained absent in 2 girls for the time period tested. In both, endogenous oestradiol levels increased to mid-follicular values. Spontaneous and regular menstrual bleedings occurred after termination of therapy. From these observations a stepwise normalisation of the functional state of the gonadostat can be expected. Similar observations exist in patients with anorexia nervosa (Keller et al. 1976) or during adolescence (Winter & Faiman 1973).

Our data on prolactin are in consent with results obtained by Frantz et al. (1972), Ehara et al. (1973) and Robyn et al. (1973), who demonstrated that oestrogens induce hyperprolactinaemia. Thus EOE and endogenous oestradiol most probably account for the PRL levels observed in our girls immediately after therapy and during the following weeks.

None of our girls developed amenorrhoea. According to reports in the literature the incidence of spontaneous amenorrhoea (Fries & Nillius 1973; Petterson et al. 1973) and so-called post-pill-amenorrhoea (Furuhjelm & Carlstrohm 1973) does not differ significantly. As far as our small number of girls tested does allow a conclusion we support these results.

27
REFERENCES

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28

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