THE EFFECT OF SHORT-TERM TESTOSTERONE TREATMENT IN BOYS WITH DELAYED PUBERTY

By

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ABSTRACT

Eight boys with severely delayed puberty without pathological cause were treated for 6 months with testosterone. This resulted in acceleration of skeletal maturation and a marked increase in height and weight. No adverse effects were found on hypothalamic-pituitary and gonadal maturation. Basal LH, FSH and testosterone levels rose to nearly adult values at follow-up within a year and pituitary responsiveness to LH-RH increased markedly.

Until recently a definite diagnosis of delayed puberty in boys could be made only in retrospect. As idiopathic delayed puberty cannot easily be separated from other causes of male hypogonadism, this makes evaluation of therapy difficult. The social and psychological disadvantages incurred by boys with retarded puberty sometimes necessitate institution of hormone therapy. It is still uncertain whether such therapy has an overall beneficial effect. Androgens promote both a rapid pubertal growth and epiphyseal closure. The latter may influence final stature adversely. A retrospective study has shown that treatment with low doses of androgens during a mean period of 5.3 months does not impair the final height attained and possibly even promotes growth (Kaplan et al. 1973). No data are available concerning the influence of this treatment on later fertility. Following administration of testosterone in high doses for 1 year to boys with excessive height, spermatogenesis recovered after
some time though this lasted 2 years in some cases (Zachmann et al. 1976). Similar data have been obtained in normal men (Mauss et al. 1975).

This study describes the effects of treatment with testosterone of 8 boys with seriously delayed puberty, on physical maturation and pituitary-gonadal function.

**MATERIALS AND METHODS**

Eight boys with delayed puberty were investigated. Delayed puberty is defined as a delay of the skeletal age of more than 2 years and a plasma testosterone below 70 ng/100 ml at the time of the initial study. The testosterone had risen in all cases to more than 400 ng/100 ml at discharge from follow-up 3-19 months after the last injection. Other causes of delayed skeletal maturation were excluded. Data of the patients are given in Table 1. In addition to a complete history and physical examination, evaluation of adrenal and thyroid functions and visual field examination were found to be within normal limits. There was no growth hormone deficiency as determined

<table>
<thead>
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<th>Patient</th>
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<td></td>
<td>1  2  3  4  5  6  7  8</td>
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<tr>
<td><strong>Before medication</strong></td>
<td></td>
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<tr>
<td>Chronological age (years)</td>
<td>15.7 16.1 15.6 17.5 17.2 18.0 14.9 15.7</td>
</tr>
<tr>
<td>Skeletal age (years)</td>
<td>13.6 12.4 12.9 15.6 18.0 11.6 10.7 10.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155 160 171 170 170 155 157 151</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>41 51 68 66 66 57 53 38</td>
</tr>
<tr>
<td>Testicular volume (ml)</td>
<td>3 3 1 4 7 2 4 3</td>
</tr>
<tr>
<td>Plasma testosterone (ng/100 ml)</td>
<td>33 44 24 34 68 22 39 44</td>
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<tr>
<td><strong>After medication</strong></td>
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<tr>
<td>Chronological age (years)</td>
<td>17.0 17.2 16.5 18.5 18.2 18.8 15.9 16.7</td>
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<tr>
<td>Skeletal age (years)</td>
<td>15.4 14.3 14.3 15.7 15.8 18.8 12.7 13.1</td>
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<tr>
<td>Height (cm)</td>
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<td>Weight (kg)</td>
<td>51 61 75 74 74 58 39 46</td>
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<tr>
<td>Testicular volume (ml)</td>
<td>4 6 5 13 12 3 8 8</td>
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<td>Plasma testosterone (ng/100 ml)</td>
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<td><strong>Final</strong></td>
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<tr>
<td>Plasma testosterone (ng/100 ml)</td>
<td>539 842 782 402 792 515 466 448</td>
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after insulin induced hypoglycaemia. All patients had a normal XY pattern. The patients were treated for 6 months with a monthly im injection of Sustanon 250®. This preparation contains 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate. No patient had complete epiphyseal closure at the time of the follow-up study when treatment had been stopped for at least 2 months. LH-RH tests were performed before medication and 8.5 till 13 months later (average interval 10.6 months) in which period Sustanon 250® was given. Tests were performed in the morning after an overnight fast. Each individual received a 100 µg iv bolus injection of LH-RH. Blood samples were drawn at 0 min before, 15, 30, 60, 120, 180 and 240 min after the injection. Serum LH and FSH were measured according to de Lange et al. (1974) and plasma testosterone was determined as described by Pratt et al. (1975). Testicular volume was measured with an orchidometer (Prader 1975). The RUS skeletal age was determined according to Tanner et al. (1975). Wilcoxon’s Rank test was used for statistical analysis. The chosen level of statistical significance (two sided) was $P = 0.05$.

**RESULTS**

The effects obtained after treatment with testosterone are shown in Table 1 and in Figs. 1–3. The increase in skeletal age surpassed that of chronological age. There was an increase in height, weight and testicular volume. Fig. 3 indicates that basal LH and FSH are higher at the time of the follow-up study.

![Fig. 1.](image)

Progression of skeletal age after treatment with Sustanon 250®
Basal testosterone level and skeletal age before and after treatment with Sustanon 250®.

Both LH-RH stimulated LH and FSH levels are higher at all times during stimulation except after 240 min. Basal testosterone is higher in the follow-up study. Before and after treatment there is a significant rise of testosterone 240 min after the bolus injection of LH-RH, even though this is not immediately apparent because of the appreciable variation in basal testosterone at the time of the follow-up. In the pre-treatment LH-RH test plasma testosterone rose from a basal level of 39 ng/100 ml (SEM ± 5) to 61 ng/100 ml (SEM ± 17) at 240 min. In the post-treatment LH-RH test the respective values were 325 ng/100 ml (SEM ± 62) and to 347 ng/100 ml (SEM ± 71).

All patients had erections and pollutions during Sustanon 250® therapy that persisted after the medication had been discontinued. All had progressive development of secondary sex characteristics. All were discharged from follow-up when puberty was completed; final testosterone values at that time are given in Table 1.

**DISCUSSION**

Recently it has become possible to predict with some confidence whether delayed puberty is truly idiopathic or has an underlying pathological cause. Using a LH-RH stimulation test both before and after administration of clo-
miphene citrate for one week a higher LH-RH induced LH peak is found in hypogonadotrophic hypogonadism while in delayed puberty the value obtained in the second test is lower (Snoep et al. 1977). Another means for differential diagnosis can be obtained with LH-RH infusion during 4 h resulting in a continuous rise of LH in boys with delayed puberty while the values obtained in hypogonadotrophic hypogonadism are falling progressively because of depletion of pituitary LH stores (de Lange et al. 1978). Because of the serious social and psychological problems experienced by boys with severely retarded puberty it would be desirable to institute treatment. There is still uncertainty

**Fig. 3.**

The effect of a 100 µg iv bolus injection of LH-RH on serum LH and FSH before and after treatment with Sustanon 250®. The results are expressed as mean ± SEM.
whether this has undesirable effects. Control studies comparing treated and untreated groups are not available. Using the approach described in this study it seems that treatment did not have an adverse influence and may have benefitted the patients. Basal LH, FSH and testosterone rose in all cases and the pituitary became more responsive to LH-RH in its secretory capacity of both LH and FSH.

It has been described that testosterone given in a dose of about 17 mg/m²/day, roughly four to five times the adult male testosterone production in puberty (Zachmann et al. 1976) and 50 mg testosterone propionate daily in adult normal men (Morse et al. 1973) results in a decrease of testicular volume and suppression of LH and FSH secretion. Prader (1975) stated that sex hormone therapy should be avoided as it suppresses the physiological increase of gonadotrophins and the increase of testicular volume. In his opinion constitutional delay of growth and adolescence in boys may present a psycho-social indication for temporary hormone therapy with testosterone.

It has been shown in recent years that an increase in adrenal androgen production precedes the start of puberty (Hopper & Yen 1975; Sizonenko & Pannier 1975; Parker et al. 1978). Especially dehydroepiandrosterone and androstenedione production are rising (Ducharme et al. 1976). This is thought to play an important role in the maturation of hypothalamic function (Ducharme et al. 1976). This in its turn results in an increase of gonadotrophins (Hopper & Yen 1975). It is conceivable that the administration of testosterone has promoted hypothalamic maturation in our patients. LH-RH stimulation tests during testosterone therapy have not been performed in our study. They might have yielded interesting results when it would have been possible to demonstrate increased LH-RH sensitivity of the pituitary. However, interpretation of such studies would have been difficult in view of the marked fluctuations of plasma testosterone during treatment with androgens and the uncertainty of the duration of their action at the hypothalamic-pituitary level.

The increase in height observed in our patients could also partly have been due to the stimulatory effect of exogenous testosterone on the secretion of growth hormone (Illig & Prader 1970). It is concluded that the short-term treatment as described in this study has had a marked beneficial effect in our patients with delayed puberty while adverse influences on endocrine sexual maturation could not be demonstrated.

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REFERENCES


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