



Universiteit
Leiden
The Netherlands

Oxandrolone in growth hormone-treated girls with Turner syndrome

Menke, L.A.

Citation

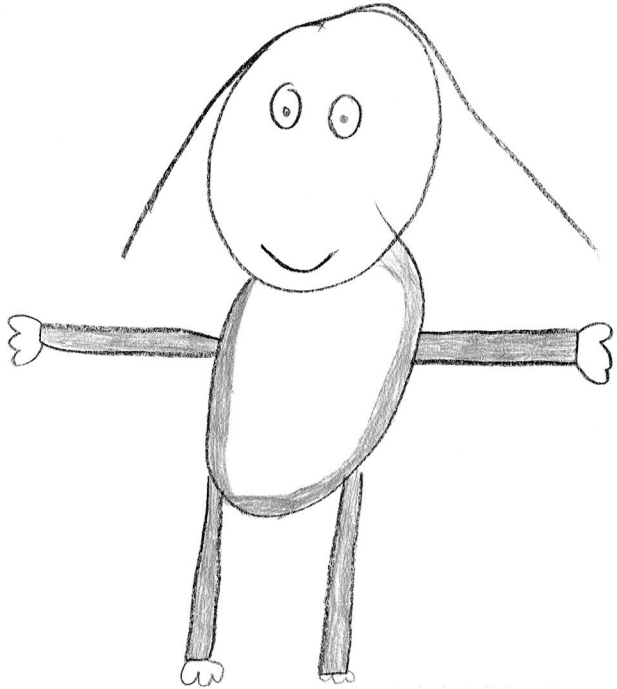
Menke, L. A. (2010, December 16). *Oxandrolone in growth hormone-treated girls with Turner syndrome*. Retrieved from <https://hdl.handle.net/1887/16251>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/16251>

Note: To cite this publication please use the final published version (if applicable).



Summary

Samenvatting

Dankwoord

Curriculum Vitae

List of publications

Summary

Turner syndrome (TS) is a disorder in females that is caused by the complete or partial absence of the second sex chromosome. The main characteristics are gonadal dysgenesis and short stature. Because the ovaries usually start to involute within 4 or 5 months of gestation in girls with TS, the majority of patients is infertile, has diminished ovarian estrogen and androgen production, and needs estrogen replacement therapy to induce pubertal maturation. Untreated adult patients are on average 20 cm shorter than healthy women, mainly due to haploinsufficiency of the Short stature Homeobox-containing (*SHOX*) gene.

Growth hormone (GH) therapy increases adult height with 5 to 12 cm, and the addition of the weak androgen oxandrolone (Ox) may further increase adult height. Ox is a synthetic, nonaromatizable anabolic steroid that is derived from testosterone. In comparison with testosterone, Ox has a high anabolic to androgenic ratio (10:1). However, in previous studies Ox dosages of ≥ 0.1 mg/kg/day had to be lowered to 0.05 and 0.06 mg/kg/day on the frequent findings of virilizing side effects and increased bone maturation. Although the recommended Ox dosage was changed into ≤ 0.05 mg/kg/day, the efficacy and safety of such dosage was unclear.

We hypothesized that, due to the effect of Ox on bone maturation, the optimal dosage with respect to adult height gain could be lower than 0.06 mg/kg/day, and therefore performed a dose-response study which was named *the Dutch Turner Oxandrolone Study*. In this randomized, placebo-controlled, double-blind study we assessed the benefit to risk ratio of Ox at a low (0.03 mg/kg/day) and previously conventional dosage (0.06 mg/kg/day) in GH-treated girls with TS. Hundred thirty-three patients were included in age group 1 (2-7.99 years), 2 (8-11.99 years), or 3 (12 -15.99 years), and treated with GH from baseline, combined with placebo (PI) or Ox 0.03 or 0.06 mg/kg/day from the age of eight, and estrogens from the age of twelve. After reaching adult height and finishing GH+Ox/PI therapy, the girls were followed for another 1.5 years.

In chapter two we assessed the effect of GH+Ox 0.03 and GH+0.06 versus GH+PI on height gain and several safety parameters. We found that the addition of either Ox 0.03 or 0.06 mg/kg/day resulted in a significant increase in height during therapy. Partly due to the increase in bone age maturation with increasing Ox dosages, adult height was reached at a younger age on both Ox dosages than on PI. Consequently, GH+Ox 0.06 did not significantly increase adult height gain. In contrast, the growth-promoting effect of GH+Ox 0.03 outweighed the increase in bone maturation, resulting in an increase in adult height gain of 2.3 cm (95% CI, 0.4 to 4.2 cm) in the intention-to-treat analysis, and 3.1 cm (95% CI, 0.5 to 5.6 cm) in the per-protocol analysis compared with GH+PI. The effect was similar in the three age groups. Partly because of the increase in bone age maturation, the duration of GH therapy was approximately 5 months shorter on GH+Ox 0.03, and 9.5 months shorter on GH+Ox 0.06 (when corrected for bone age at starting GH). As a result, the cumulative costs of GH were respectively 10,100 and 13,500 euro less than the mean cumulative costs of 161,200 euro on GH+PI (a significant difference for group GH+Ox 0.06; a trend was found for group GH+Ox 0.03). Forty-two percent of the patients on GH+Ox 0.06 reported virilization (including subjective voice deepening, clitoral enlargement, and/or hirsutism), and about half of these patients decided to discontinue Ox preliminarily for that reason. The addition of Ox to GH slowed breast development. Although breast stage SDS caught up after discontinuing GH+Ox and increasing estrogen dosages, it was still lower on GH+Ox 0.03 than on GH+PI at the end of the follow-up period: the median Tanner breast stage was 4 (range 2-5) in group GH+Ox 0.03 versus a median of 5 (range 4-5) in group GH+PI. IGF-I levels were more frequently increased on GH+Ox than on GH+PI, whereas the increase in IGF-I levels and IGF-I/IGFBP-3 ratio was not significantly different between the dosage groups. The addition of Ox did not increase blood pressure. One girl, who already had an impaired glucose tolerance at baseline, had impaired glucose tolerance and an elevated HbA1c (7.7%) after two years of GH+Ox 0.03 therapy. She therefore discontinued GH+Ox, after which HbA1c and glucose levels returned to normal. The HbA1c levels of all other girls remained normal, and none of the girls developed diabetes mellitus type 1 or 2.

In chapter three we concluded that the voices of untreated girls with TS are relatively high-pitched and that the addition of Ox to GH increases voice deepening in a dose-dependent way. Although most voice frequencies remained within the normal range, they occasionally became lower than -2 SDS, especially on GH+Ox 0.06 mg/kg/day. These data confirmed the findings in chapter one that Ox 0.03 has an acceptable safety profile, whereas Ox 0.06 results in virilization in a considerable number of patients. Although objective voice deepening was greater in patients reporting subjective voice deepening, we showed that a questionnaire concerning subjective voice changes does not seem a reliable measure for undesirable voice deepening.

In chapter four, the effects of Ox on body proportions and body composition are described. We found that in GH-treated girls with TS, Ox 0.06 increases sitting height and tends to increase biacromial distance and decreases biiliacal distance, while Ox 0.03 significantly decreases biiliacal distance compared with height. Furthermore, Ox 0.06 reduced subcutaneous fat mass, and both Ox dosages increased muscle mass, resulting in a fat mass that was lower and muscle masses that were higher than in healthy girls, respectively. Whereas we considered the effects of Ox 0.03 on body proportions and composition acceptable, the effects of Ox 0.06 confirmed our opinion that this dosage should not be prescribed in TS.

The effect of Ox on glucose metabolism is described in chapter five. We concluded that insulin sensitivity indices decrease during GH therapy but return to pretreatment levels after discontinuing therapy. In contrast to previously studied higher Ox dosages, no significant side effects with respect to glucose metabolism were encountered when adding Ox at a dosage of 0.06 or 0.03 mg/kg/day to GH. Fasting glucose levels even decreased on GH+Ox compared with GH+PI.

The effect of Ox on psychological and behavioral characteristics is presented in chapter six. We showed that Ox at a dosage of 0.03 mg/kg/day or 0.06 mg/kg/day does not cause evident psychological virilizing side effects in the area of behavior, aggression, romantic and sexual interest, mood, and gender role in GH-treated girls with TS. Problem behavior was frequently found in untreated girls with TS, but

seemed to decrease during therapy. Whether this represented an effect of GH and/or estrogen therapy could not be clarified. Total and internalizing problem behavior remained increased throughout the study period.

In chapter seven we discuss the benefit to risk ratio of either Ox 0.03 or Ox 0.06 in GH-treated girls with TS. We conclude that Ox in a previously conventional dose (0.06 mg/kg/day) has limited efficacy and gives rise to virilizing side effects, and we therefore discouraged its use. The addition of low-dose Ox (0.03 mg/kg/day) increases height during therapy, modestly increases adult height gain, and has a fairly good safety profile, except for a small deceleration in breast development. We therefore recommend that in patients considering the increment in height gain more important than the small deceleration of breast development, Ox 0.03 mg/kg/day may be added to GH to increase height.