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**Effect of oxandrolone and timing of pubertal induction on final height in Turner syndrome -
final analysis of the United Kingdom randomised placebo-controlled trial**

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Abstract

The United Kingdom Turner syndrome (TS) study examined the effect on final height of oxandrolone 0.05 mg/kg/day (maximum dose 2.5mg) versus placebo from 9 years of age; and delaying ethinylestradiol induction of puberty by two years from 12 (E12) to 14 (E14) years in growth hormone-treated girls with TS. The study ran from 1999 to 2013. By 2011, 82 of 92 participants had reached final height and an interim analysis using the Super-Imposition by Translation And Rotation (SITAR) model showed significant increases in final height with both oxandrolone and E14. The analysis has been repeated now that all 92 patients have reached final height. Oxandrolone still significantly increased final height by 4.1 cm (95% CI 1.6 to 6.6 cm, n=92) compared with 4.6 cm previously. However, the E14 effect was no longer significant at 2.7 cm (CI -0.8 to 6.1 cm, n=56) compared with 3.8 cm previously. (147 words)

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The United Kingdom (UK) Turner Study, conducted across the UK between 1999 and 2013, was a randomised, double-blind, placebo-controlled trial of growth promoting treatment in Turner syndrome, with an interim report published in 2011.¹ The study aims were to examine the impact on final height of a) oxandrolone versus placebo treatment from 9 years; and b) delaying estrogen induction of puberty from 12 to 14 years, in girls with Turner syndrome who were receiving a standard dose of growth hormone. Interim analysis showed a large effect of oxandrolone and a smaller effect of late pubertal induction on final height. The purpose of the present paper is to report the reanalysis of the UK Turner study now that all patients have reached final height.

Methods

As reported previously¹, the study protocol involved two randomisations in girls with Turner syndrome, confirmed on karyotype, who were receiving growth hormone (GH) in the standard dosage of 10mg/m²/wk, equivalent to 55 µg/kg/day). The first randomisation at 9 years was to receive either oxandrolone 0.05mg/kg/day (max daily dose 2.5mg) or placebo until final height. The second randomisation at 12 years was for girls with serum follicle stimulating hormone levels > 10 u/L (reflecting significant ovarian insufficiency) to receive oestrogen in the form of ethinylestradiol at either 12 or 14 years. Girls receiving ethinylestradiol at 12 years (E12) took 2 µg daily for one year, followed by 4 µg daily for the second year, and 4-monthly increments to 6, 8 and 10 µg during the third year. Girls receiving ethinylestradiol at 14 years (E14) took placebo for 2 years until 14 years, then followed the same incremental ethinylestradiol protocol; the oestrogen randomisation code was broken at 15 years to allow the introduction of progesterone treatment. Girls enrolled aged >12.25 years were termed the 'late group' and automatically assigned to receive ethinylestradiol at 14 years. The primary outcome measure was final height, [defined as height velocity <1 cm/year and bone age >15.5 years. Details of characteristics at](#)

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[enrolment including initial age, height SDS and breakdown of karyotype can be found in the 2011 interim report.¹](#)

Reanalysis of the 92 girls was carried out using an updated version of the SuperImposition by Translation And Rotation (SITAR) model.² Using this shape invariant model, mean curves were fitted to each of the four treatment arms. Curves for individuals are matched to the mean curve by shifting their curve up-down (representing body size), left-right (representing growth tempo), and shrinking or stretching the age scale (reflecting height velocity).

The study had been approved previously by the Scotland A Research Ethics Committee (formerly Multi-centre Research Ethics Committee for Scotland) [Ref. 98/0/92] as well as by local research ethics committees at participating centres. Written informed consent from parents and assent from the girls at enrolment had also been obtained.

Results

[A flow diagram showing the outcome in the 106 girls originally enrolled and the distribution of the 92 girls reaching final height according to randomisation is shown in Figure 1. Following the interim analysis published in 2011, no further patients had withdrawn and the 10 patients who were still growing had now reached final height.](#)

For the primary randomization, 43 girls had received oxandrolone and 49 placebo. Fifty-six girls then underwent second randomisation at 12 years, with 28 receiving oestrogen and 28 receiving placebo until 14 years. Nineteen girls were in the late group and 17 did not require pubertal induction with oestrogen.

Final height outcome in the 92 girls [who remained in the study is shown in the Table](#). Mean (SD) final height was 151.8 (6.3) cm – almost identical to that at interim analysis: 151.8 (6.4) cm.

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Change in final height SDS was greatest for the 24 girls receiving oxandrolone: + 0.7 SDS for those randomised to E14 (n=13) and + 0.6 SDS for those randomised to E12 (n=11).

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Fitted curves in the oxandrolone/placebo and E12/E14 groups are shown in Figure 2. SITAR analysis showed that oxandrolone increased both size/amplitude of growth (p=0.02) and growth velocity (p< 0.001). E14 showed a near-significant delay in tempo (p=0.07) and had a negative effect on velocity (p=0.0005).

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Oxandrolone still showed a significantly although slightly reduced increase in final height by 4.1 cm (95% CI 1.6 to 6.6 cm, n=92; p=0.002) compared with 4.55 cm at interim analysis. However, the effect of delaying pubertal induction from 12 to 14 years was no longer significant: 2.7 cm (CI -0.8 to 6.1 cm, n=56; p=0.13) compared with 3.75 cm previously.

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Table Final height in 92 girls completing the UK Turner study, by treatment group. The red box indicates final height according to the interaction between randomisation 1 (oxandrolone or placebo) and randomisation 2 (ethinylestradiol at 12 or 14 years). Height standard deviation scores (Ht SDS) are based on the UK 1990 reference³. Delta (Δ) height refers to the change in Ht SDS from baseline (i.e. study enrolment) to final height.

Characteristics	Randomised to oestrogen at 12 years		Randomised to oestrogen at 14 years		Late group (oestrogen at 14 years)		No oestrogen needed		Total
	Oxandrolone	Placebo	Oxandrolone	Placebo	Oxandrolone	Placebo	Oxandrolone	Placebo	
	(n=11)	(n=17)	(n=13)	(n=15)	(n=9)	(n=10)	(n=10)	(n=7)	(n=92)
Age (years)	16.1 (1.5)	16.3 (0.9)	16.8 (0.8)	17.1 (0.8)	17.1 (1.0)	17.9 (1.0)	15.1 (0.9)	15.3 (1.0)	16.5 (1.3)
Height (cm)	154.4 (3.9)	148.1 (7.2)	154.2 (5.7)	152.4 (6.6)	155.3 (4.3)	148.9 (6.0)	151.9 (6.0)	150.3 (6.3)	151.8 (6.3)
Ht SDS	-1.3 (0.7)	-2.4 (1.2)	-1.5 (0.9)	-1.8 (1.1)	-1.3 (0.7)	-2.4 (1.0)	-1.4 (0.9)	-1.9 (0.9)	-1.8 (1.0)
Δ Ht SDS	0.6 (0.5)	-0.1 (0.7)	0.7 (0.9)	-0.1 (0.7)	0.7 (0.8)	0.4 (0.8)	0.5 (0.9)	0.1 (0.8)	0.3 (0.8)

Discussion

The positive effect of oxandrolone on final height in Turner syndrome is in keeping with work from the Netherlands⁴ and the USA⁵, although the magnitude of the effect differs between these studies, possibly due to differences in treatment regimen and participant characteristics⁶.

Unfortunately, the subsequent European production of oxandrolone has not resumed since its cessation in 2008. As a result, oxandrolone, although available through import from the USA, remains possible only at considerable cost, limiting its application to girls aged > 9 years in whom the growth response to growth hormone therapy is disappointingly low despite good compliance, as evidenced by high-normal IGF-1 levels.

The interim analysis had suggested that delaying pubertal induction with oral ethinylestradiol from 12 to 14 years provided significant benefit. However, the difference of 2.7 cm found on reanalysis was no longer significant. A possible explanation for the reduced effect of starting pubertal induction at 14 years is that the oxandrolone and oestrogen at 12 years interventions encouraged more accelerated growth, as shown by the SITAR analysis, and that as a result the girls in these treatment arms finished growing earlier, with those in the placebo arms catching up only later. Although late pubertal induction could have a positive effect on final height, even without reaching significance, there can now be little support for delaying pubertal induction beyond 12 years. This is because 12 years is already relatively late compared to natural processes, and there is now evidence for better psychosocial development⁷ and better uterine health⁸ with timely induction.

[Since the 92 girls in this UK Turner study reached final height, several guidelines containing recommendations for estrogen therapy have been published. These include the consensus guidelines from the 2016 Cincinnati International Turner Syndrome Meeting,⁹ recommendations from the British Society for Paediatric Endocrinology and Diabetes for pubertal induction,¹⁰ and a minireview by the Turner syndrome Working Group \(TSWG\) of the European Society for](#)

[Paediatric Endocrinology.](#) ¹¹ [All these publications recommend natural estrogen in the form of 17β-estradiol, given by either the oral or transdermal route, rather than synthetic oral estrogen such as ethinylestradiol. The TSWG proposes a 3-year induction programme, usually beginning at 11 years and detailing both tablet and matrix patch protocols which allow the delivery of incremental estradiol doses based on body weight.](#)¹¹

In conclusion, the beneficial effect of oxandrolone on final height in Turner's syndrome is confirmed. By contrast, delaying pubertal induction beyond 12 years did not significantly improve final height in the final analysis of this cohort. However, the option of delaying pubertal induction in girls with Turner syndrome who are diagnosed particularly late (e.g. after 12 years) in whom short stature is a major concern should be discussed with the family.¹¹ (975 words)

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Figure legends

Figure 1 Flow diagram of outcome in 106 girls enrolled in the UK Turner study, by treatment group. First randomisation to Oxandrolone or placebo is shown in red and allocation to treatment or not with ethinylestradiol is shown in green: second randomisation to receive ethinylestradiol or placebo at 12 years, treatment at 14 years in placebo group, no treatment required, and automatic assignment to estrogen at 14 years in girls enrolled aged ≥ 12.25 years (late group). Withdrawals are shown in white.

Figure 2 SITAR fitted summary height curves by trial arm for randomisation 1 [oxandrolone vs placebo from 9 years] (left panel) and randomisation 2 (ethinylestradiol for pubertal induction at 12 vs 14 years) (right panel)

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[Competing interests: none declared](#)

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