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Clinical Research Article

Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment

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Abstract

Context: Transgender adolescents can receive gonadotropin-releasing hormone analogues (GnRH) and gender-affirming hormone therapy (GAHT), but little is known about effects on growth and adult height. This is of interest since height differs between sexes and some transgender girls wish to limit their growth.

Objective: This work aims to investigate the effects of GnRHa and GAHT on growth, and the efficacy of growth-reductive treatment.

Methods: This retrospective cohort study took place at a specialized tertiary gender clinic. A total of 161 transgender girls were treated with GnRHa and estradiol at a regular dose (2 mg) or high growth-reductive doses of estradiol (6 mg) or ethinyl estradiol (EE, 100-200 μg). Main outcome measures included growth, adult height, and the difference from predicted adult height (PAH) and target height.

Results: Growth velocity and bone maturation decreased during GnRHa, but increased during GAHT. Adult height after regular-dose treatment was 180.4 ± 5.6 cm, which was 1.5 cm below PAH at the start GnRHa (95% CI, 0.2 cm to 2.7 cm), and close to target height (–1.1 cm; 95% CI, –2.5 cm to 0.3 cm). Compared to regular-dose treatment, high-dose estradiol and EE reduced adult height by 0.9 cm (95% CI, –0.9 cm to 2.8 cm) and 3.0 cm (95% CI, 0.2 cm to 5.8 cm), respectively.

Conclusion: Growth decelerated during GnRHa and accelerated during GAHT. After regular-dose treatment, adult height was slightly lower than predicted at start of GnRHa, likely due to systematic overestimation of PAH as described in boys from the general population, but not significantly different from target height. High-dose EE resulted in greater reduction of adult height than high-dose estradiol, but this needs to be weighed against possible adverse effects.

Key Words: transgender, adolescents, puberty blockers, estradiol, growth, adult height

Abbreviations: ACOG, Amsterdam Cohort of Gender Dysphoria; BA, bone age; CA, chronological age; CAIS, complete androgen insensitivity syndrome; EE, ethinyl estradiol; GAHT, gender-affirming hormone therapy; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone analogues; IGF-1, insulin-like growth factor 1; IQR, interquartile range; LC-MS/MS, liquid chromatography–tandem mass spectrometry; PAH, predicted adult height; PS, puberty suppression.

Gender dysphoria is defined as distress caused by incongruence between one's gender identity and the sex assigned at birth. These feelings concerning gender identity can already occur in early childhood (1). When gender incongruent feelings persist or arise in adolescence, physical changes associated with puberty that are incongruent with gender identity may increase dysphoric feelings (2). To reduce distress, medical treatment can be considered (3).

When carefully executed, early diagnosis and treatment of gender dysphoria can be beneficial for transgender youth. Puberty suppression (PS) using gonadotropin-releasing hormone analogues (GnRHa) from an early pubertal stage can prevent irreversible physical changes such as lowering of the voice and enlargement of the Adams apple. Another irreversible characteristic associated with gender is height. In the Dutch population, men reach a mean adult height of 183.8 cm, which is more than 13 cm taller than women (170.7 cm) (4). Many adolescents and their parents have questions about the effect of PS and gender-affirming hormone therapy (GAHT) on adult height. However, only few data are available on the effects of this treatment on growth and adult height in transgender adolescents. Ghelani et al (5) and Schagen and

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colleagues (6) reported a significant decrease in height SD score (SDS) in transgender girls during GnRHa treatment. In both studies, most individuals were in late puberty at the start of PS. In a study by Hannema et al (7), estradiol was shown to induce growth acceleration resulting in an adult height of –0.2 SDS compared to male references and +1.9 SDS compared to female references. However, data on predicted adult height before the start of treatment or on target height were not included in that study, and thus it was not clear if treatment had influenced growth and adult height.

Some transgender girls wish to reduce their growth in order to reach an adult height within the normal female range. Surgical treatment, that is, an epiphysiodesis, can be used to limit growth (8, 9). According to the Endocrine Society Guidelines, transgender girls may also be treated with a high dose of estrogen to reduce growth (3). However, the effectiveness of this medical treatment option has been studied only in constitutionally tall girls (10).

The aim of this study is to describe the effects of GnRHa and estradiol treatment on growth in transgender girls, and to evaluate if a high dose of estradiol or ethinyl estradiol (EE) reduces growth and adult height.

Materials and Methods

Participants

The study used data from the Amsterdam Cohort of Gender Dysphoria (ACOG) database, a large, retrospective clinical data set from individuals who were seen at the Center of Expertise on Gender Dysphoria in Amsterdam from 1972 until December 2018 (11). For the present study we analyzed data of transgender girls if they had initiated GnRHa treatment before age 18 years, received estrogen therapy, and had reached adult height, defined as bone age (BA) greater than or equal to 16 years assessed according to the Greulich and Pyle male standard (12), or growth velocity of less than 2 cm/year and assessed in those who had reached age 18 years at time of data collection. A subset of these data has previously been published by Schagen et al (6). Individuals with genetic disorders known to affect growth or who had discontinued treatment before adult height was reached were excluded. To collect additional data on the effect of high-dose EE treatment, data from all individuals who had received such treatment but had reached adult height after 2018 (and whose adult height data were therefore not in the ACOG database) were also included. The entire cohort was then divided into 2 groups based on growth potential. The pubertal group consisted of individuals with a BA of less than 16 years at the start of PS. The postpubertal group, which served as a control group, consisted of individuals with a BA greater than or equal to 16 years and those who had finished growth based on clinical data and therefore had no BA measurements at the start of PS.

Treatment Protocol

To confirm the diagnosis of gender dysphoria according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth and later fifth edition (13, 14), all individuals were assessed by a mental health professional. Medical treatment consisted of subcutaneous or intramuscular triptorelin (Decapeptyl-CR (Ferring) 3.75 mg every 4 weeks or Pamorelin (Ipsen) 11.25 mg every 10-12 weeks) to suppress puberty. From age 15 to 16 years, GAHT was initiated. Regular-dose estrogen treatment consisted of daily oral tablets of 17β-estradiol with a starting dose of 5 microgram/kilogram/day (μg/kg/d), which was increased every 6 months by 5 μg/kg/d up to an adult dose of 2 mg/d. In those who had nearly completed endogenous puberty, the starting dose was 1 mg, which was increased to 2 mg/d after 6 months (3). If a very tall adult height was expected, substantial growth potential remained, and the adolescent wished to limit growth, growth-reductive treatment with high-dose estrogen was offered. Two different treatment options were used depending on the preference of the treating physician. In the first approach, the 17β-estradiol dose was increased to a dose of 6 mg/d in a period of 10 weeks. The second approach consisted of daily oral tablets of EE in a dose of 100 or 200 μg. In some cases, both treatment options were used consecutively. For analyses, individuals were classified according to the treatment that was used longest. If both treatments had been prescribed for a period 6 months or longer, the treatment group was defined as "combined" and data from these individuals were not included in the estrogen regimen–specific analysis. None of the adolescents included in the present study underwent epiphysiodesis to limit growth. GnRHa was continued during estrogen therapy until gonadectomy had been performed. Only those aged 18 years or older who had used estradiol treatment for at least 1 year were eligible for a gonadectomy.

Measurements

Height and weight were evaluated at the start of PS and then every 3 to 6 months. Height was measured using a wall-mounted stadiometer, and weight was measured using a digital floor scale. Height SDS was calculated according to Dutch male reference data (4) and body mass index SDS was calculated according to reference data from Cole et al (15). Target height was calculated as follows: target height = (paternal height + maternal height)/2 + 6.5 (16). BA was determined at the start of PS and GAHT and, depending on clinical need, repeated yearly to every 2 years until (near) adult height was reached. To determine BA, x-rays of the left hand were analyzed according to Greulich and Pyle using male references (12). The PAH was determined using BoneXpert Adult Height Predictor version 3.0. according to male gender and White North European ethnicity.

Laboratory Investigations

Serum estradiol levels were measured using liquid chromatography–tandem mass spectrometry (LC-MS/MS; VUmc) with an interassay coefficient of variation of 7% and a limit of quantitation of 20 pmol/L from July 2014. Serum estradiol levels from before this date were converted to LC-MS/MS values as described by Wiepjes et al (17).

Until June 2006, insulin-like growth factor 1 (IGF-1) was measured on the Nichols Advantage Specialty System (Nichols Institute Diagnostics) using the 2-site immunochemiluminometric technique. Between June 2006 and April 2012, the Immulite 2500 laboratory assay (Siemens Medical Solutions Diagnostics) was used. For conversion, the formula Immulite = 0.99*Advantage + 1.2 was used. Since April 2012, a chemiluminescence immunoassay (LIAISON, DiaSorin) was used to analyze IGF-1 (interassay coefficient of variation 7%). The formulas Liaison = 1.040*Immulite +

1.785 (if < 30 nmol/L) and Liaison = 0,692*Immulite + 8.8 (if > 30 nmol/L) were used for conversion. After June 2013, IGF-1 serum levels were harmonized, which resulted in 20% lower values. Therefore all values from before this date were multiplied by 0.8.

Statistical Analyses

The statistical analyses were performed using STATA 15.1 (StataCorp). Data are presented as number (%), mean ± SD when normally distributed, or median (interquartile range; IQR) when not normally distributed. Linear regression analysis was used to analyze differences in continuous baseline characteristics between the treatment schedules.

Growth velocity was compared between the first and second year of PS treatment using mixed-model regression analysis with measurements clustered within participants. The change in height SDS during PS was evaluated using mixed-model regression analyses where effect modification of duration of PS was applied. Bone age minus chronological age (BA-CA) and PAH were compared between start of PS and start of GAHT using mixed-model regression analyses. Duration of PS in years as effect modifier was applied in the mixed-model regression analysis of BA-CA.

Mixed-model regression analysis was used to evaluate differences in height SDS between start GAHT and adult height. Efficacy of growth reductive treatment was analyzed by comparing the difference between PAH at the start of GAHT and adult height between the treatment groups. To minimize differences at baseline between the 3 treatment groups, 2 subgroup analyses were performed: 1 in individuals with a PAH of 180 cm or greater and 1 in individuals with a BA less than or equal to 14 years at the start of GAHT. Difference between target height and adult height was analyzed with linear regression; adjustment for BA at the start of GAHT was performed separately.

Ethics

The protocol for data collection for the ACOG data set was assessed by the local medical ethical committee, which determined that the Medical Research Involving Human Subjects Act (WMO) did not apply to this data collection. Owing to the retrospective design of the study and the size of the cohort, informed consent was not required. The 10 individuals treated with EE from whom additional data were collected all provided informed consent for the use of their data in this study.

Results

The ACOG data set contained 8831 individuals, of whom 5350 were birth-assigned males. After selection for GnRHa initiation before age 18 years, estrogen use, and age 18 years or older at the last visit from which data were available, a total of 176 participants remained. Fifteen individuals were excluded, 9 because of missing BA at the start of PS, 3 because of genetic disorders known to affect growth, 2 because of missing height measurements, and 1 because of temporary discontinuation of treatment before reaching adult height.

Baseline Characteristics

A total of 161 individuals were included, of whom 88 with growth potential formed the pubertal group. Data from this group will be described in detail. Data from the other 73 individuals (postpubertal group) are briefly described at the end of the results section. Baseline characteristics are presented in Table 1. Participants who received growth reductive treatment were younger, had a less advanced Tanner stage at the start of PS, and their target height and PAH were higher than in transgender girls treated with a regular dose.

Puberty Suppression

The mean duration of PS was 2.4 ± 0.8 years. Individuals had an average growth velocity of 5.3 ± 2.2 cm/year in the first year of treatment. This decreased to 3.5 ± 1.3 cm/year in the second year (decrease –1.9 cm; 95% CI, –2.4 cm to –1.4 cm). This resulted in a continuous decrease of height SDS during PS (–0.37/year; 95% CI, –0.47 to –0.27) (Figs. 1A and 2). At baseline, BA was within the physiological range for CA with a BA-CA of –0.2 ± 0.9 years. During PS bone maturation decreased, resulting in a BA delayed by 1.6 ± 0.8 years at the start of GAHT. A longer duration of PS resulted in a greater delay of bone age (–0.5 years/year of PS; 95% CI, –0.8 to –0.2). PAH increased by 1.5 cm (95% CI, 0.5 cm to 2.6 cm) between the start of PS and start of GAHT.

Regular-dose Estradiol Treatment

Transgender girls treated with a regular estradiol dose (n = 47) had a mean duration of PS of 2.3 ± 0.8 years and initiated GAHT at age 16.2 ± 0.5 years. Individuals on a 2 mg dose had average serum estradiol levels with a median of 130 pmol/L (IQR, 105 to 183) (n = 24). Growth velocity in the first year of GAHT was 2.8 ± 1.8 cm/year, which decreased to 1.4 ± 1.2 cm/year in the second year. From the start of GAHT, height increased by 5.9 cm (95% CI, 5.7 cm to 6.2 cm) to an adult height of 180.4 ± 5.6 cm (male height SDS –0.48 ± 0.78; female height SDS + 1.55 ± 0.89) (Table 2). Height SDS increased by 0.17 cm (95% CI, 0.04 cm to 0.29 cm) from the start of GAHT to adult height but remained below height SDS at start PS (Figs. 1B and 2). Adult height was 1.5 ± 4.2 cm lower than PAH at start PS, and 1.8 ± 2.2 cm below PAH at start GAHT, but just above target height by 1.1 ± 4.5 cm (Fig. 3).

Growth-reductive Estradiol Treatment

A total of 22 transgender girls were treated with 6 mg estradiol. They had a mean duration of PS of 2.3 ± 0.6 years and were aged 15.4 ± 0.8 years at start GAHT. In 5 individuals, the high dose was initiated within 6 months from the start of GAHT. In the remaining 17 participants, a high dose was prescribed 1.4 ± 0.5 years after the initial start of regular-dose estradiol treatment. Average serum estradiol levels at the time of treatment with a 6 mg dose were significantly higher than the regular group, with a median of 597 pmol/L (IQR, 507 to 679 pmol/L) (n = 14). From the start of GAHT, height increased by 9.9 cm (95% CI, 9.6 cm to 10.2 cm) to an adult height of 185.3 ± 5.6 cm (male height SDS 0.21 ± 0.80; female height SDS + 2.33 ± 0.90) (see Table 2). Height SDS increased by 0.30 cm (95% CI, 0.01 cm to 0.58 cm) between the start of GAHT and adult height. Adult height was 0.3 ± 4.3 cm above PAH at the start of PS and 2.7 ± 4.3 cm below PAH at the start of GAHT, but only 1.3 cm (IQR, –5.3 cm to 3.4 cm) below target height (Fig. 3).

Growth-reductive Ethinyl Estradiol Treatment

Eleven transgender girls received EE to limit growth. The mean duration of PS was 2.6 ± 0.9 years. GAHT

Table 1. Baseline characteristics of the pubertal group (those with bone age < 16 years) stratified by estrogen treatment regimen, and of the postpubertal group (those who had nearly/completely finished linear growth)

	Pubertal group				Postpubertal group	Total
	Regular dose	High dose	EE	Combined		
Participants	47	22	11	8	73	161
Age at start of PS, y	13.5 (13.2 to 14.5)	13.1 (12.1 to 13.6)	12.4 (12.1 to 14.0)	12.6 (11.9 to 13.5)	16.8 (16.1 to 17.3)	14.7 (13.3 to 16.7)
Tanner stage at start of PS						
G2	7 (16)	9 (41)	6 (55)	4 (50)	0 (0)	26 (16)
G3	14 (31)	11 (50)	3 (27)	2 (25)	1 (1)	31 (19)
G4	9 (19)	1 (5)	1 (9)	2 (25)	3 (4)	16 (10)
G5	17 (36)	1 (5)	1 (9)		64 (88)	83 (52)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	5 (7)	5 (3)
Height at start of PS, cm	165.8 ± 8.4	163.4 ± 7.2	160.8 ± 6.3	161.0 ± 6.1	176.7 ± 6.9	169.5 ± 9.7
Missing	0 (0)	0 (0)	0 (0)	0 (0)	7 (10)	7 (4)
Bone age at start of PS, y	13.5 (13.0 to 14.0)	13.0 (12.5 to 13.5)	13.0 (12.0 to 13.5)	13.0 (12.0 to 13.25)	18 (17 to 18)	13.3 (13.0 to 13.9)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	38 (52)	38 (24)
Predicted adult height at start of PS, cm	182.9 (177.0 to 186.7)	184.2 (180.7 to 188.6)	185.2 (180.4 to 187.5)	184.3 (182.8 to 187.0)	177.9 (171.9 to 184.1)	181.4 (177.1 to 186.5)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	39 (53)	39 (24)
Target height, cm	180.0 (176.5 to 184.0)	184.0 (181.0 to 189.5)	180.3 (178.5 to 186.3)	184.8 (182.0 to 187.5)	179.3 (177.0 to 183.5)	181.0 (178.0 to 185.5)
Missing	5 (11)	1 (5)	3 (27)	0 (0)	31 (42)	40 (25)

Data are presented as number (%), mean ± SD, or median (interquartile range).
Abbreviations: combined, both EE and 6 mg had been prescribed consecutively for a period 6 months or more; EE, ethinyl estradiol 100-200 μg/d to reduce growth; high, high-dose estradiol of 6 mg/d to reduce growth; GAHT, gender-affirming hormone therapy; PS, puberty suppression; regular, regular pubertal induction regimen up to estradiol 2 mg/d.

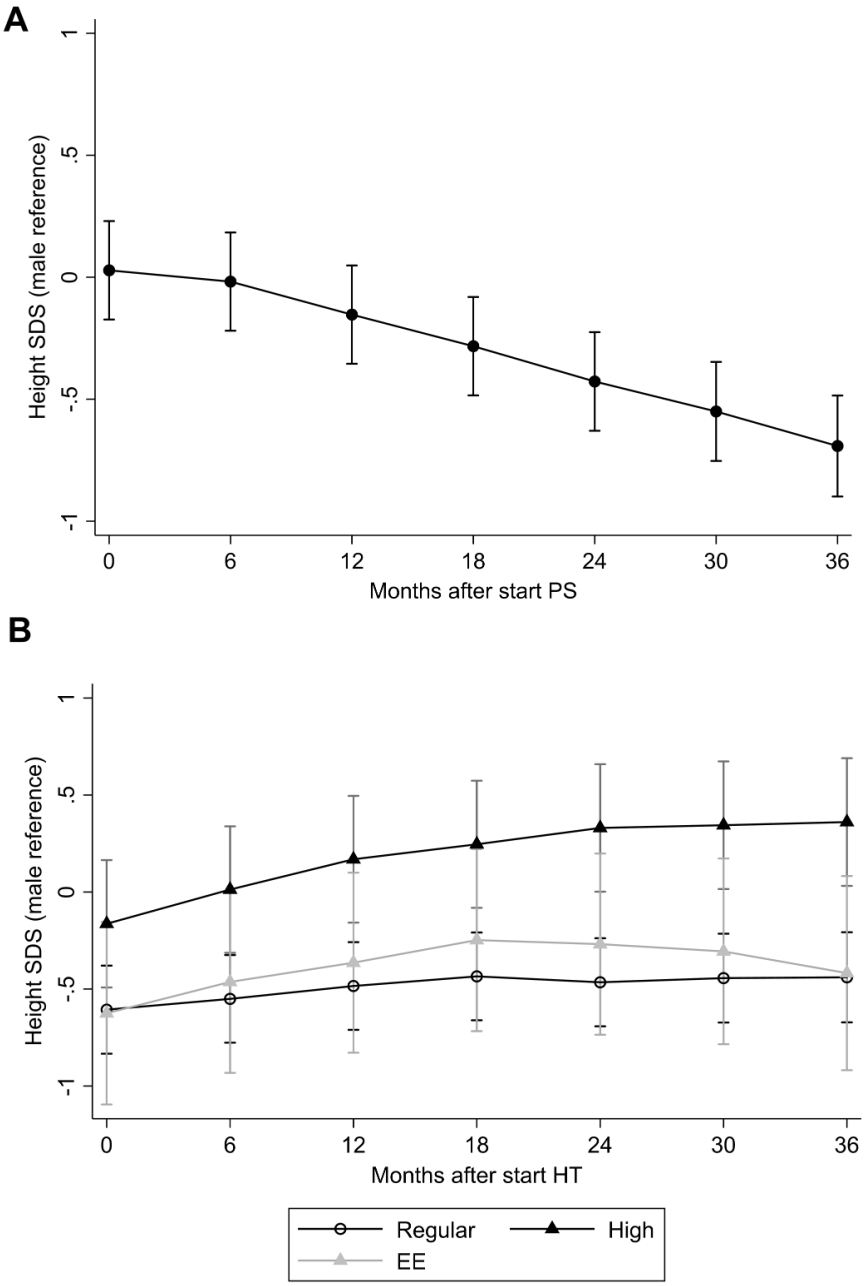

Figure 1. Height SD score (SDS) during A, puberty suppression (PS), and B, gender-affirming hormone therapy (HT), in 3 different treatment groups (regular-dose estradiol, high-dose estradiol, and ethinyl estradiol [EE]).

was initiated at a mean age of 15.6 ± 0.5 years. Seven individuals started with EE within 6 months from the start of GAHT; the other 4 subjects started with EE 1.5 ± 0.4 years after the start of GAHT. Two participants were treated with 100 µg EE, 3 with 200 µg EE, and 6 started with 100 µg, which was increased to 200 µg EE. Height increased by 7.6 cm (95% CI, 7.1 cm to 8.0 cm) during GAHT to an adult height of 180.1 ± 5.8 cm (male height SDS –0.53 ± 0.82; female height SDS 1.48 ± 0.93) (see Table 2). Height SDS increased by 0.05 cm (95% CI, –0.23 cm to 0.33 cm). Adult height was 4.7 ± 4.1 cm below PAH at the start of PS, 4.8 ± 3.8 cm below PAH at the start of GAHT, and slightly below target height by 1.8 ± 7.3 cm (see Fig. 3).

Efficacy of Growth Reduction

Adult height was lower than PAH at the start of GAHT in all groups, but this difference was 3.0 cm larger in transgender girls treated with EE when compared to individuals who received regular-dose estradiol treatment (95% CI, 0.2 cm to 5.8 cm) (see Fig. 3). This difference was considered the achieved growth reduction. High-dose estradiol did not result in a significant growth reduction (0.9 cm; 95% CI, –0.9 cm to 2.8 cm). Because BA differed between the groups and this might influence the accuracy of adult height prediction, we performed a subgroup analysis in participants with a BA of 14 years or less at the start of GAHT. This also showed a larger growth reduction in the EE group (2.7 cm [95% CI, –0.7 cm to 6.2 cm], n = 6) than in the high-dose estradiol

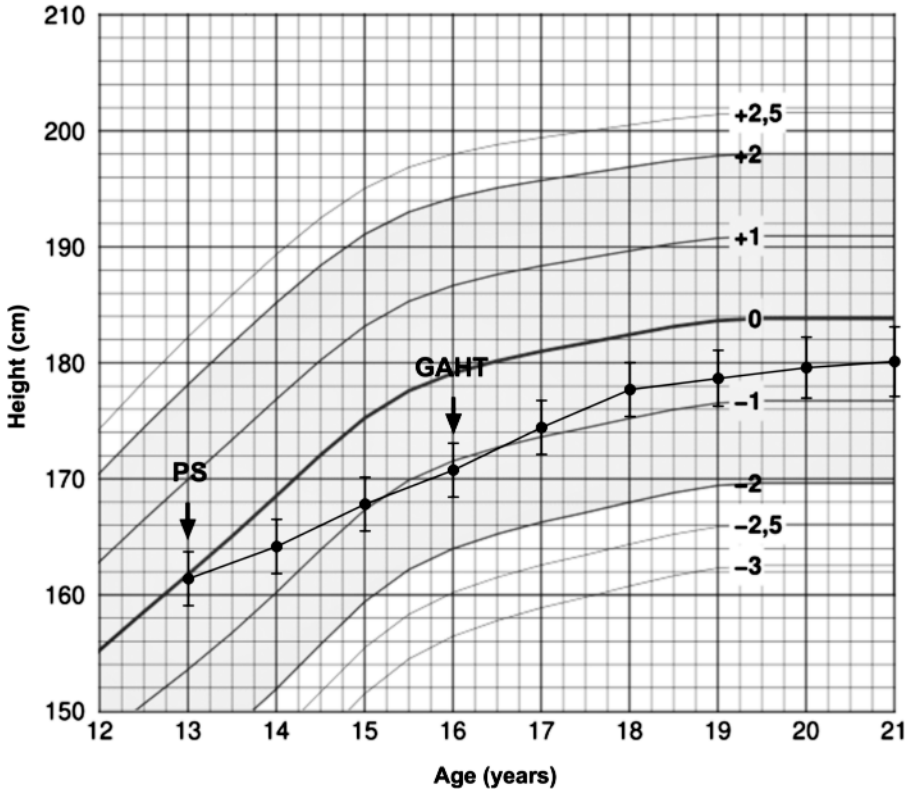

Figure 2. Mixed-model analysis of height during puberty suppression (PS) and gender-affirming hormone therapy (GAHT) of 20 individuals who initiated PS at age 13 and GAHT at age 16 and were treated with regular-dose estradiol, plotted on the growth chart for Dutch boys from Schönbeck et al (4).

Table 2. Growth during estrogen treatment in the different treatment groups

	Regular-dose estradiol, 2 mg	High-dose estradiol, 6 mg	High vs regular (95% CI)	EE 100-200 g	EE vs regular (95% CI)
No. of participants	47	22		11	
Duration PS, y	2.3 ± 0.8	2.3 ± 0.6	0.0 (–0.4 to 0.4)	2.6 ± 0.9	0.2 (–0.3 to 0.7)
Bone age start of GAHT, y	14.5 ± 0.8	13.8 ± 0.4	–0.7 (–1.1 to –0.3)	13.8 ± 0.4	–0.8 (–1.3 to –0.2)
PAH at start of GAHT	181.6 ± 6.1	187.5 ± 6.3	5.9 (2.1 to 9.8)	185.8 ± 9.6	4.2 (–1.6 to 10.0)
Missing[a]	14 (30)	4 (18)		5 (45)	
Height, cm					
Start PS	165.8 ± 8.4	163.4 ± 7.2	–2.5 (–6.5 to 1.6)	160.8 ± 6.3	–5.0 (–10.2 to 0.2)
Start GAHT	174.8 ± 6.8	175.9 ± 6.4	1.1 (–2.3 to 4.5)	172.9 ± 5.5	–1.9 (–6.3 to 2.4)
Adult height	180.4 ± 5.6	185.3 ± 5.6	4.8 (4.2 to 5.5)	180.1 ± 5.8	0.3 (–0.8 to 1.3)
Male height SDS					
Start of PS	–0.15 ± 0.83	0.23 ± 1.09	0.38 (–0.09 to 0.85)	–0.09 ± 0.86	0.06 (–0.55 to 0.67)
Start of GAHT	–0.63 ± 0.83	–0.08 ± 1.08	0.59 (0.12 to 1.05)	–0.59 ± 0.65	0.04 (–0.55 to 0.64)
Adult height	–0.48 ± 0.78	0.21 ± 0.80	0.69 (0.28 to 1.10)	–0.53 ± 0.82	0.05 (–0.58 to 0.47)
Target height	–0.54 (–1.03 to 0.02)	0.02 (–0.40 to 0.80)	0.68 (0.60 to 0.77)	–0.50 (–0.75 to 0.34)	0.28 (0.12 to 0.44)

Data are presented as mean ± SD or as median (interquartile range).
Abbreviations: EE, ethinyl estradiol 100-200 µg/d to reduce growth; GAHT, gender-affirming hormone therapy; high dose, high-dose estradiol of 6 mg/d to reduce growth; PAH, predicted adult height; PS, puberty suppression; regular, regular pubertal induction scheme up to estradiol 2 mg/d; SDS, SD score.

group (0.7 cm [95% CI, –1.7 cm to 3.2 cm], n = 17), although in these small groups neither difference was statistically significant. A subgroup analysis in participants with a PAH greater than or equal to 180 cm at the start of GAHT showed a growth reduction of 3.9 cm (95% CI, 0.5 cm to 7.2 cm) in individuals treated with EE (n = 5) and 0.9 cm (95% CI, –1.4 cm to 3.2 cm) in individuals who received high-dose estradiol (n = 15). Adult height was below target height in both growth-reductive treatment groups. When compared to the group with regular-dose estradiol treatment, this difference was more pronounced in the participants treated with EE (2.9 cm; 95% CI, –1.4 cm to 7.1 cm) than those treated with

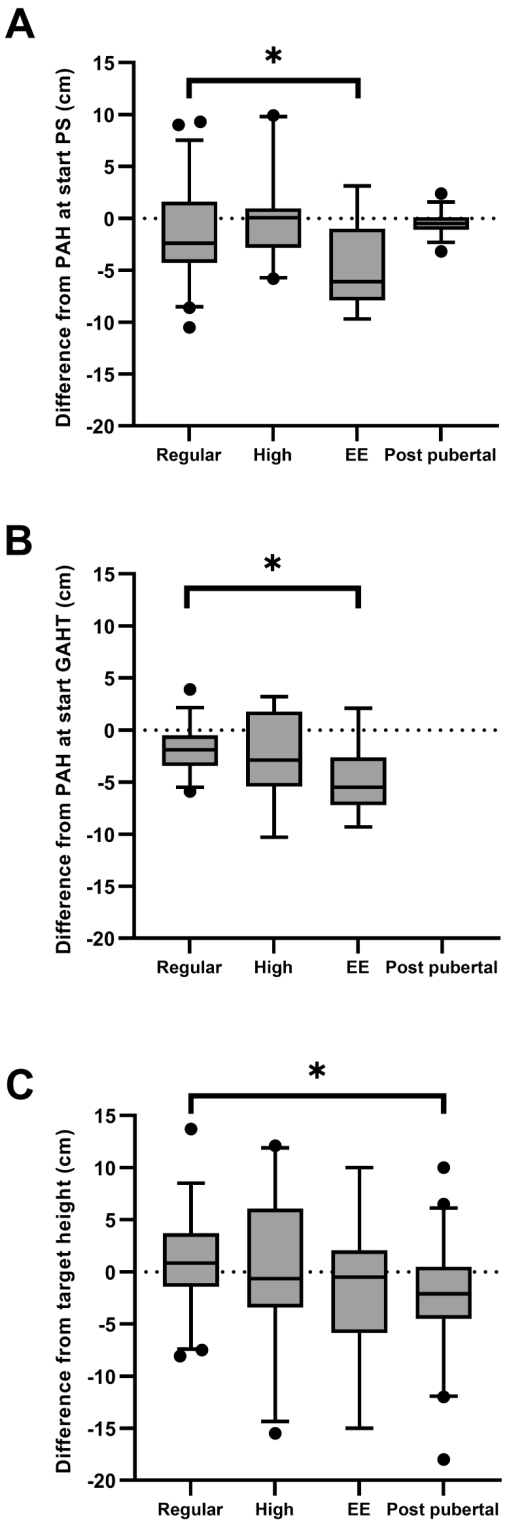

Figure 3. Shown are the differences A, between adult height and predicted adult height (PAH) at start of puberty suppression (PS); B, between adult height and PAH at start of gender-affirming hormone therapy (GAHT); and C, between adult height and target height in the different treatment groups (regular-dose estradiol, n = 47; high-dose estradiol, n = 22; ethinyl estradiol [EE], n = 11) and in the postpubertal group who had already reached (near) adult height before the start of any treatment and can therefore be seen as a control group (n = 73). Negative values indicate that adult height was lower than predicted. Boxes represent interquartile range, whiskers represent 5th to 95th percentile, and circles represent outliers. * value less than .05.

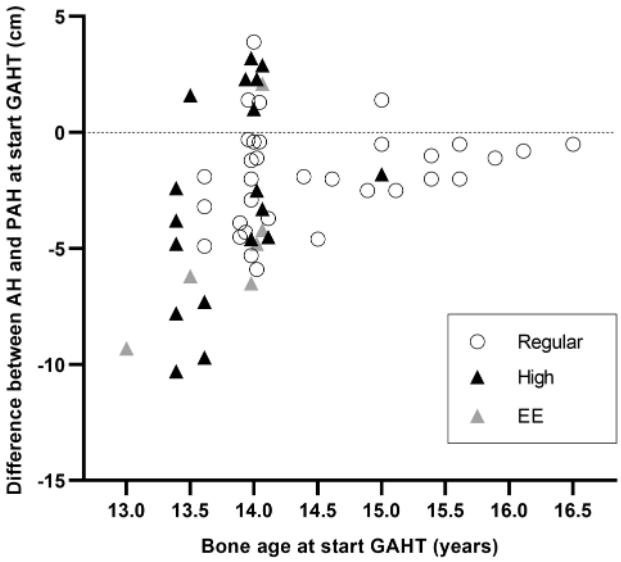

Figure 4. The difference between adult height (AH) and predicted adult height (PAH) at start gender-affirming hormone therapy (GAHT) by bone age in the different treatment groups (regular-dose estradiol, high-dose estradiol, ethinyl estradiol [EE]). Negative values indicate that AH was lower than predicted.

a high dose of estradiol (0.8 cm; 95% CI, –2.2 cm to 3.8 cm). These values were similar after adjustment for BA at the start of GAHT (data not shown). Individual growth curves are shown in Supplementary Figs. 1A to 1C (18).

Timing of Treatment

Individuals who started GAHT at a lower BA reached an adult height that was 1.6 cm/year (95% CI, 0.6 to 2.7) further below PAH at the start of GAHT (Fig. 4).

Serum Insulin-like Growth Factor 1 During Treatment

Besides a mild increase in IGF-1 serum levels in the first 6 months, no changes were observed during PS. During GAHT, IGF-1 levels decreased slightly (Fig. 5). No significant differences between participants treated with the regular and the high dose of estradiol were observed. IGF-1 levels from individuals treated with EE are not shown because those were available in only one person.

Adolescents With Little/No Growth Potential (Postpubertal Group)

A total of 73 transgender girls had little to no growth potential at the start of PS. In 22 participants (30%) height did not increase during treatment. Height at the start of PS was missing in 7 individuals. Height increased in 44 individuals (66%) by a median of 1.0 cm (0.5 cm to 2.0 cm) until an adult height of 177.8 ± 6.7 cm (male height SDS –0.85 ± 0.94; female height SDS + 1.12 ± 1.07) was reached. Adult height was 2.7 cm lower (95% CI, –7.9 cm to –0.4 cm) compared to adult height in the regular-dose group. Furthermore, adult height was 0.5 ± 1.0 cm below PAH at the start of PS (n = 34). Adult height was 2.4 ± 5.0 cm below target height (n = 42); this difference was significantly larger compared to the group with regular-dose treatment (3.4 cm; 95% CI, 1.1 cm to 5.7 cm; Fig. 3C).

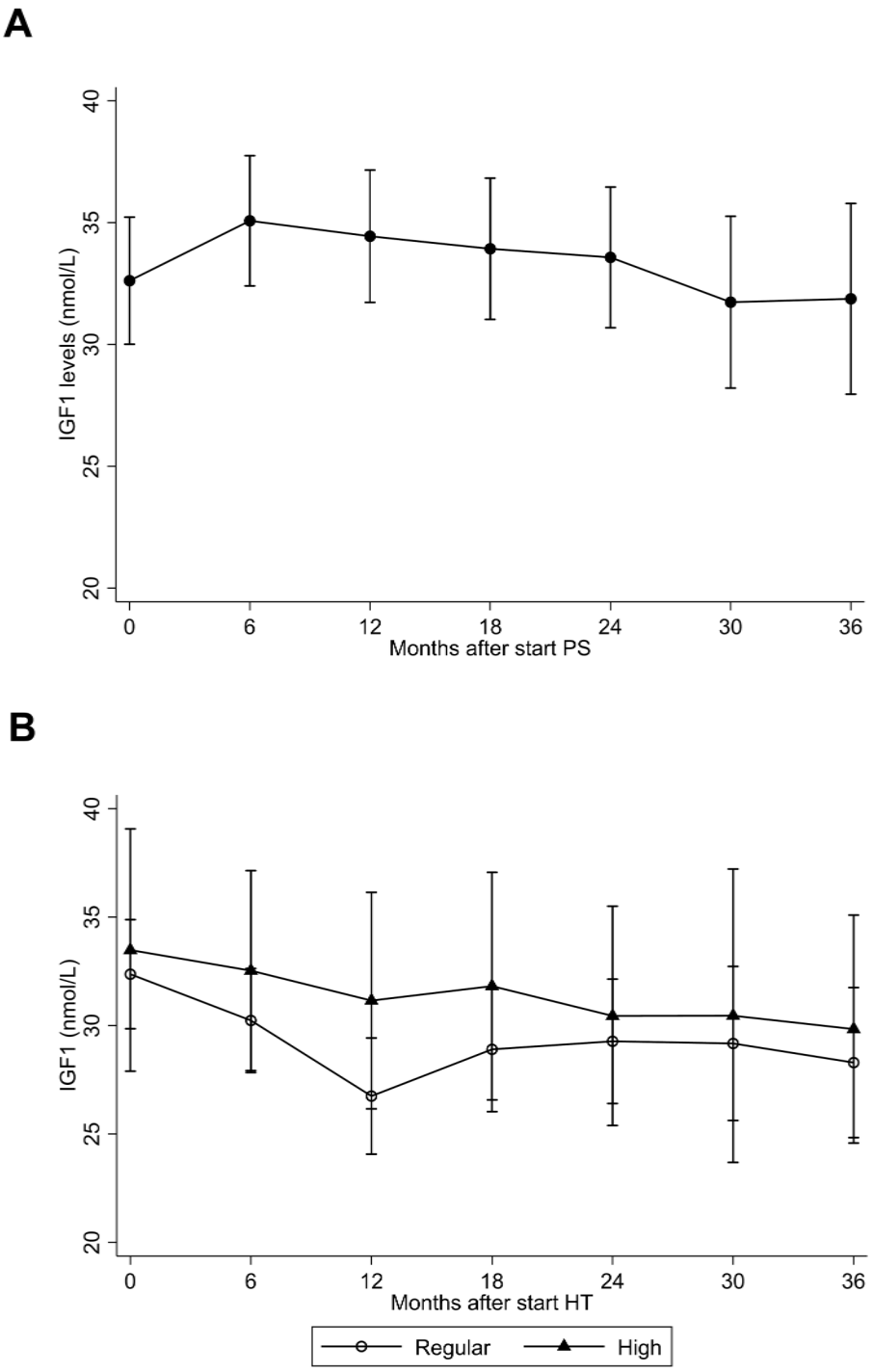

Figure 5. Insulin-like growth factor 1 (IGF-1) serum levels during A, puberty suppression (PS), and B, gender-affirming hormone therapy (GAHT), in 2 different treatment groups (regular-dose estradiol, high-dose estradiol). IGF-1 levels from individuals treated with ethinyl estradiol are not shown because those were available in only one person.

Discussion

In this study, we investigated the effects of both GnRHa and estrogen treatment on growth and adult height in transgender girls. As expected, treatment with GnRHa resulted in a decrease of growth velocity and bone maturation. During GAHT, growth velocity and bone maturation increased. In the group that received the regular treatment, that is, PS followed by normal-dose estradiol, adult height was close to PAH at baseline and close to target height. In contrast, treatment with high-dose EE resulted in growth reduction, whereas high-dose estradiol did not significantly reduce growth.

During the PS phase, a decrease in height SDS of –0.45 was observed. This is comparable to the findings of Ghelani et al (5), who described a height SDS decrease of 0.17 in the first year of treatment. Besides a decrease in height SDS, bone maturation also decelerated during PS. While BA was close to CA at start PS, BA was delayed by –1.6 years at the start of GAHT. These first findings of bone maturation rate during PS

in the transgender population are in line with several studies in boys with central precocious puberty that also reported a decrease in bone maturation during treatment with GnRHa (19-21).

After the decrease of height SDS during PS, a slight increase was observed during GAHT. The fact that this is an observational uncontrolled study makes it challenging to determine the effect of the treatment on adult height. We have analyzed the effect on adult height in 4 ways: 1) the change in height SDS from start of treatment to adult height; 2) the difference between adult height and PAH at the start of treatment; 3) the difference between adult height and target height; and 4) the comparison of adult height and difference between adult height and target height between those who started treatment before and after completing growth (pubertal and postpubertal group).

In transgender girls treated with a regular estradiol dose, adult height SDS remained 0.32 below height SDS at the start of PS. This may be because girls with an expected tall height, who may have ended up at a height SDS that was higher than that at the start of PS, received growth reduction, so that the remaining group consisted of girls who ended up with a slightly lower height SDS. This is supported by the finding that adult height was close to what was predicted at the start of PS in this treatment group. Adult height was 1.5 ± 4.2 cm lower than predicted, which is comparable to findings from a validation study of the BoneXpert adult height prediction method in White boys, where for BAs 11 to 15 years adult height was on average between 0.5 cm lower to 1.5 cm higher than predicted (22).

Another finding that suggests that the treatment does not affect adult height is the small difference between adult height and target height of 1.1 ± 4.5 cm. Interestingly, individuals who had nearly/completely finished their growth before the start of treatment (postpubertal group) reached a shorter adult height than individuals from the pubertal group. In addition, in the postpubertal individuals mean adult height was below target height. This was significantly different from those who had started treatment earlier and had received a regular dose of estradiol, where adult height was 1.1 ± 4.5 cm above target height. This suggests that treatment may actually have a small positive effect on adult height. However, target height was available for only 58% of individuals from the postpubertal group so these results need to be interpreted with caution. It is possible that physicians inquired about parental height more often in shorter adolescents. Thus, taken together, analysis of change in height SDS during treatment, comparison of adult height to PAH and target height, and comparison of adult height in groups treated before and after completion of linear growth indicates that although PS and GAHT alter the growth pattern, they have little effect on adult height.

With regard to growth reduction, the finding that adult height was 3.0 cm further below PAH in the group that received EE than in the regular-dose estradiol group indicates a growth-reductive effect of EE. This is the first report on high-dose EE reducing adult height in transgender girls, but the treatment has previously been used in constitutionally tall girls. Normann and colleagues (23) described a difference between PAH and adult height ranging from 3.1 cm (95% CI, 2.5 cm to 3.7 cm) to 5.2 cm (95% CI, 4.2 cm to 6.2 cm) in 98 individuals treated with 100 µg EE with a BA of 13 years or greater and less than 12.5, respectively. The study by de Waal et al (10) showed a difference of 1.7 ± 2.2 cm (CA ≥ 15 years) to 5.9 ± 3.0 cm (CA ≤ 11 years) in girls treated with 100 to 300 µg EE. This is comparable to our finding that in the EE-treated group adult height was 4.7 ± 4.1 cm below PAH at the start of PS.

In tall boys treated with high-dose testosterone, adult height was 2.9 ± 3.7 cm (CA = 15 years) to 10.6 ± 11.3 cm (CA ≤ 12 years) lower than PAH according to B&P. However, after correction for CA, BA, and height prediction, the growth-reductive effect was smaller, and in those with BA greater than 14.1 years no growth reduction was seen at all (10). The median BA in transgender girls at the start of GAHT was 13.8 years; based on the data from de Waal et al (10) high-dose testosterone treatment would have resulted in a growth reduction of only approximately 1 cm.

The larger growth reduction we observed after high-dose EE treatment might be explained by the important role that estrogen plays in epiphyseal fusion. Several studies revealed this importance by describing unfused epiphyses and extremely delayed BA in cisgender men with estrogen deficiency or estrogen insensitivity (24, 25). Although testosterone is partially converted to estradiol, high-dose EE will result in much higher estrogen levels than high-dose testosterone treatment and this most likely accounts for more effective epiphyseal closure (26). In several girls, EE treatment was started only after they had received regular-dose estradiol treatment for some time up to 2 years. The treatment would likely have been more effective in reducing adult height if it had been started as soon as GAHT was initiated, as we found a negative correlation between BA at the start of GAHT and the difference between AH and PAH.

In this study, EE was prescribed in doses of 100 to 200 µg. Numbers were not sufficient to study if the growth-reductive effect was dose dependent. However, several studies in constitutionally tall girls showed a comparable effect of 100 µg and higher doses of EE, but more side effects with the higher doses (23, 27). In this study, side effects of high-dose estradiol and EE were not evaluated. Earlier studies described nausea, vomiting, and headache as the most common side effects of EE (28, 29). Thromboembolic events have been described but were mainly observed in individuals with other risk factors for thromboembolisms (28-30). Concerns regarding an increased cancer risk have been expressed but the limited data available on this subject are not conclusive (31). In cisgender girls EE is no longer used to limit growth because it has been found to reduce later fertility (32). The risk of infertility due to gender-affirming treatment is an important topic for transgender adolescents too, but it currently is not clear if this risk is different after estradiol compared to EE treatment.

Because of the increased risk of venous thromboembolism with the use of high-dose EE, treatment with high-dose estradiol was introduced in our clinic as an alternative method to reduce growth. However, the present study shows that this does not significantly reduce adult height. The delayed introduction of the high dose, often more than 1 year after the start of GAHT, may have limited its efficacy. However, the higher potency of EE compared to estradiol might also explain the difference in effect between high-dose EE and high-dose estradiol. The "high" dose of 6 mg estradiol is likely not bioequivalent to 100 to 200 µg of EE. Kirk et al (33) stated that 1 µg of EE is an approximately 4- to 10-fold higher dose than 1 mg of 17β-estradiol. Another, more effective but also

more invasive, alternative to reduce growth is epiphysiodesis, which results in a growth reduction of approximately 7 cm, depending on BA (8, 9).

In addition to side effects, other outcomes of estrogen treatment may differ between regular-dose estradiol and growth-reductive treatment. For transgender girls, breast development generally is one of the most important treatment goals and future studies should investigate the effect of different treatment regimens on outcomes such as breast size, shape, and development of striae. Another topic for future research is the effect of different treatment strategies on bone mineral density.

During PS, there was no change in IGF-1 serum levels except for a mild transient increase during the first months. This shows that the increasing level of sex hormones can induce the onset of the IGF-1 increase but that this increase continues despite the absence of these hormones. This is in line with findings in individuals who were treated with GnRHa for precocious puberty where no or little effect on IGF-1 levels was found (34, 35). However, a decrease in free IGF-1 has been reported, which might explain the reduced growth rate (36, 37). During GAHT we observed a decrease of IGF-1 as have previously been described during oral estradiol and EE treatment but levels remained within the physiological range (38, 39).

This study also provides insight into the regulation of growth and the role of sex hormones vs sex chromosomes. The finding that transgender girls, who have XY chromosomes and are treated with estradiol, reach an adult height close to the population mean for males suggests a minor role for sex hormones. This is in line with findings from studies in individuals with complete androgen insensitivity syndrome (CAIS) or XY complete gonadal dysgenesis in whom adult height was closer to male target height or average height in the male population (40, 41). This supports the idea that genetic factors, rather than sex hormones, are important in the regulation of growth (41, 42). However, the fact that in the transgender girls treatment with estradiol was initiated after a prolonged period of PS should not be overlooked. As mentioned before, estradiol has an important role in closure of the growth plates. In transgender girls, this occurs at a later age than during physiological female puberty, after height has continued to increase slowly but consistently during PS. The importance of the timing of estrogen exposure is apparent from a study in women with CAIS by Han et al (43), who described a correlation between shorter adult height and younger age of gonadectomy and introduction of estradiol treatment. This suggests that earlier initiation of estradiol in transgender girls might result in shorter adult height.

This study has strengths and limitations. Strengths are the large cohort, the standardization of the 3 different treatment regimens, and the inclusion of a control group of transgender adolescents who had nearly or completely finished linear growth before the start of treatment. A limitation is the retrospective character of the study with some missing data. Another limitation is the delayed introduction of the growth-reductive treatment in some individuals and the difference in baseline characteristics between the 3 treatment groups. However, we tried to minimize the effect of these differences by performing subgroup analyses in groups that were more comparable. Last, side effects were not assessed in the present study; this is an important topic for future research.

Conclusion

With the results of this study, it is possible to counsel transgender girls about the effect of PS and GAHT on growth. Growth and bone maturation decelerate during PS and then accelerate again after the start of GAHT. Overall, regular treatment seems to have little effect on adult height. When predicting adult height after PS, at the start of GAHT, it is important to realize that BoneXpert slightly overestimates adult height. If tall transgender girls have a strong wish for hormonal growth reduction, treatment with 100 µg EE is recommended after counseling about possible side effects. A 6 mg dose of estradiol is not effective to reduce growth and therefore not recommended. Future research is needed to assess whether treatment with a higher dose of 200 µg leads to a larger growth reduction than 100 µg EE. In addition, side effects of EE in transgender girls should be investigated. Finally, it is important not to pathologize tall stature and also discuss the possibility of refraining from any growth-reductive intervention.

Disclosures

The authors have nothing to disclose.

Data Availability

The data set generated during and analyzed during the present study is not publicly available because of privacy regulations.

References

1. Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci*. 2010;47(2):132-138. https://doctorsonly.co.il/wp-content/uploads/2011/12/2010_2_7.pdf
2. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;16(4):499-516. Doi:10.1177/1359104510378303
3. Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903. Doi:10.1210/jc.2017-01658
4. Schönbeck Y, Talma H, van Dommelen P, *et al*. The world's tallest nation has stopped growing taller: the height of Dutch children from 1955 to 2009. *Pediatr Res*. 2013;73(3):371-377. Doi:10.1038/pr.2012.189
5. Ghelani R, Lim C, Brain C, Fewtrell M, Butler G. Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. *J Pediatr Endocrinol Metab*. 2020;33(1):107-112. Doi:10.1515/jpem-2019-0045
6. Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. *J Sex Med*. 2016;13(7):1125-1132. Doi:10.1016/j.jsxm.2016.05.004
7. Hannema SE, Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA. Efficacy and safety of pubertal induction using 17β-estradiol in transgirls. *J Clin Endocrinol Metab*. 2017;102(7):2356-2363. Doi:10.1210/jc.2017-00373
8. Goedegebuure WJ, Jonkers F, Boot AM, *et al*. Long-term follow-up after bilateral percutaneous epiphysiodesis around the knee to reduce excessive predicted final height. *Arch Dis Child*. 2018;103(3):219-223. Doi:10.1136/archdischild-2017-313295
9. Odink RJ, Gerver WJ, Heeg M, Rouw CW, van Waarde WM, Sauer PJ. Reduction of excessive height in boys by

bilateral percutaneous epiphysiodesis around the knee. *Eur J Pediatr*. 2006;165(1):50-54. Doi:10.1007/s00431-005-1722-z
10. de Waal WJ, Greyn-Fokker MH, Stijnen T, *et al*. Accuracy of final height prediction and effect of growth-reductive therapy in 362 constitutionally tall children. *J Clin Endocrinol Metab*. 1996;81(3):1206-1216. Doi:10.1210/jcem.81.3.8772601
11. Wiepjes CM, Nota NM, de Blok CJM, *et al*. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): trends in prevalence, treatment, and regrets. *J Sex Med*. 2018;15(4):582-590.
12. Greulich WW, Pyle SI. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. 2nd ed. Stanford University Press; 1959.
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2018.
14. American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. American Psychiatric Association; 2000.
15. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240-1243. Doi:10.1136/bmj.320.7244.1240
16. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2-9 years allowing for heights of parents. *Arch Dis Child*. 1970;45(244):755-762. Doi:10.1136/adc.45.244.755
17. Wiepjes CM, de Blok CJ, Staphorsius AS, *et al*. Fracture risk in trans women and trans men using long-term gender-affirming hormonal treatment: a nationwide cohort study. *J Bone Miner Res*. 2020;35(1):64-70. Doi:10.1002/jbmr.3862
18. Boogers LS, Wiepjes CM, Klink DT, *et al*. Supplementary data for: "Transgender girls grow tall: adult height is unaffected by GnRH analogue and estradiol treatment." Figshare. Deposited June 1, 2022. https://doi.org/10.6084/m9.figshare.19949483
19. Shim YS, Lim KI, Lee HS, Hwang JS. Long-term outcomes after gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty. *PLoS One*. 2020;15(12):e0243212. Doi:10.1371/journal.pone.0243212
20. Hümmelink R, Oostdijk W, Partsch CJ, Odink RJ, Drop SL, Sippell WG. Growth, bone maturation and height prediction after three years of therapy with the slow release GnRH-agonist Decapeptyl-Depot in children with central precocious puberty. *Horm Metab Res*. 1992;24(3):122-126. Doi:10.1055/s-2007-1003273
21. Boepple PA, Mansfield MJ, Wierman ME, *et al*. Use of a potent, long acting agonist of gonadotropin-releasing hormone in the treatment of precocious puberty. *Endocr Rev*. 1986;7(1):24-33. Doi:10.1210/edrv-7-1-24
22. Martin DD, Schittenhelm J, Thodberg HH. Validation of adult height prediction based on automated bone age determination in the Paris Longitudinal Study of healthy children. *Pediatr Radiol*. 2016;46(2):263-269. Doi:10.1007/s00247-015-3468-8
23. Normann EK, Trygstad O, Larsen S, Dahl-Jørgensen K. Height reduction in 539 tall girls treated with three different dosages of ethinyloestradiol. *Arch Dis Child*. 1991;66(11):1275-1278. Doi:10.1136/adc.66.11.1275
24. Smith EP, Boyd J, Frank GR, *et al*. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N Engl J Med*. 1994;331(16):1056-1061. Doi:10.1056/nejm199410203311604
25. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *J Clin Endocrinol Metab*. 1995;80(12):3689-3698. Doi:10.1210/jcem.80.12.8530621
26. Cutler GB Jr. The role of estrogen in bone growth and maturation during childhood and adolescence. *J Steroid Biochem Mol Biol*. 1997;61(3-6):141-144. Doi:10.1016/S0960-0760(97)80005-2
27. Bartsch O, Weschke B, Weber B. Oestrogen treatment of constitutionally tall girls with 0.1 mg/day ethinyl oestradiol. *Eur J Pediatr*. 1988;147(1):59-63. Doi:10.1007/bf00442613
28. de Waal WJ, Torn M, de Muinck Keizer-Schrama SM, Aarsen RS, Drop SL. Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. *Arch Dis Child*. 1995;73(4):311-315. Doi:10.1136/adc.73.4.311
29. Trygstad O. Oestrogen treatment of adolescent tall girls; short term side effects. *Acta Endocrinol Suppl (Copenh)*. 1986;279(113):170-173.
30. Werder EA, Waibel P, Sege D, Flury R. Severe thrombosis during oestrogen treatment for tall stature. *Eur J Pediatr*. 1990;149(6):389-390. Doi:10.1530/acta.0.112s170
31. Benyi E, Kieler H, Linder M, *et al*. Risks of malignant and non-malignant tumours in tall women treated with high-dose oestrogen during adolescence. *Horm Res Paediatr*. 2014;82(2):89-96. Doi:10.1159/000360137
32. Venn A, Bruinsma F, Werther G, *et al*. Oestrogen treatment to reduce the adult height of tall girls: long-term effects on fertility. *Lancet*. 2004;364(9444):1513-1518. Doi:10.1016/s0140-6736(04)17274-7
33. Kirk JMW, Wickramasuriya N, Shaw NJ. Estradiol: micrograms or milligrams. *Endocrinol Diabetes Metab Case Rep*. 2016;2016(1):150096. Doi:10.1530/edm-15-0096
34. Muratoglu Sahin N, Peltek Kendirci HN, Çetinkaya S, Savaş Erdeve , Aycan Z. The alteration of IGF-1 levels and relationship between IGF-1 levels and growth velocity during GnRH analogue therapy. *J Pediatr Endocrinol Metab*. 2020;33(1):113-120. Doi:10.1515/jpem-2018-0482
35. Kanety H, Karasik A, Pariente C, Kauschansky A. Insulin-like growth factor-I and IGF binding protein-3 remain high after GnRH analogue therapy in girls with central precocious puberty. *Clin Endocrinol (Oxf)*. 1996;45(1):7-12. Doi:10.1111/j.1365-2265.1996.tb02053.x
36. Juul A, Scheike T, Nielsen CT, Krabbe S, Müller J, Skakkebaek NE. Serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 levels are increased in central precocious puberty: effects of two different treatment regimens with gonadotropin-releasing hormone agonists, without or in combination with an antiandrogen (cyproterone acetate). *J Clin Endocrinol Metab*. 1995;80(10):3059-3067. Doi:10.1210/jcem.80.10.7559897
37. Müller J, Juul A, Andersson AM, Sehested A, Skakkebaek NE. Hormonal changes during GnRH analogue therapy in children with central precocious puberty. *J Pediatr Endocrinol Metab*. 2000;13(Suppl 1):739-746. Doi:10.1515/jpem.2000.13.s1.739
38. Torres-Santiago L, Mericq V, Taboada M, *et al*. Metabolic effects of oral versus transdermal 17β-estradiol (E_2): a randomized clinical trial in girls with Turner syndrome. *J Clin Endocrinol Metab*. 2013;98(7):2716-2724. Doi:10.1210/jc.2012-4243
39. Rooman RPA, De Beeck LO, Martin M, van Doorn J, Mohan S, Du Caju MVL. Ethinylestradiol and testosterone have divergent effects on circulating IGF system components in adolescents with constitutional tall stature. *Eur J Endocrinol*. 2005;152(4):597-604. Doi:10.1530/eje.1.01880
40. Papadimitriou DT, Linglart A, Morel Y, Chaussain JL. Puberty in subjects with complete androgen insensitivity syndrome. *Horm Res*. 2006;65(3):126-131. Doi:10.1159/000091592
41. Ogata T, Matsuo N. The Y specific growth gene(s): how does it promote stature? *J Med Genet*. 1997;34(4):323-325. Doi:10.1136/jmg.34.4.323
42. Smith DW, Marokus R, Graham JM Jr. Tentative evidence of Y-linked statural gene(s). Growth in the testicular feminization syndrome. *Clin Pediatr (Phila)*. 1985;24(4):189-192. Doi:10.1177/000992288502400402
43. Han TS, Goswami D, Trikudanathan S, Creighton SM, Conway GS. Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. *Eur J Endocrinol*. 2008;159(2):179-185. Doi:10.1530/eje-08-0166