Hormone Research in Paediatrics

Horm Res Paediatr , DOI: 10.1159/000542553
Received: September 25, 2023
Accepted: November 8, 2024
Published online: November 29, 2024

# Contribution of Sex Steroids in Management of Tall Stature: Is it Effective or Not?

Akcan N, Verdecchia F, Hindmarsh PC, Dattani M

ISSN: 1663-2818 (Print), eISSN: 1663-2826 (Online)
https://www.karger.com/HRP
Hormone Research in Paediatrics

**Contribution of Sex Steroids in Management of Tall Stature: Is it Effectiveor Not?**

Nese Akcan[1,2], Federica Verdecchia[2,3], Peter C. Hindmarsh[4], Mehul Dattani[2,5]
[1]Department of Pediatric Endocrinology, Faculty of Medicine, Near East University, Nicosia, Turkish Republic of Northern Cyprus,
[2]Endocrinology Department, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK
[3] Endocrinology Department, Bambino Gesù Children's Hospital, Roma,Italy
[4] Department of Pediatric Endocrinology, University College London Hospitals NHS Foundation Trust
[5]Genetics and. Genomic Medicine Programme, UCL GOS Institute of Child Health, London, UK

**Short Running Title: Therapy with Sex Steroids in Tall Stature**

**Correspondence:**
Nese Akcan
E-mailaddress: nese.akcan@med.neu.edu.tr
Address: Department of Pediatric Endocrinology, Faculty of Medicine, Near East University, East Avenue, Nicosia, Cyprus
ORCID: https://orcid.org/0000-0003-2583-5736
Telephone: +9 0392 675 10 00 [1388] Fax number: +90 [392] 2236464

Word count:4113 Abstract word count:256
Number of tables:5
Number of figures:-
Disclosure of funding: None
Conflicts of interest: None declared

**Keywords: Estradiol Treatment, Ethinyloestradiol, Sex steroid hormones, Tall stature, Testosterone**

**Abstract**

**Introduction:** Reduction in adult height by high-dose sex steroids was introduced decades ago. Here, we present the impact of lower doses of sex steroids on the predicted adult height in children with tall stature.

**Methods:** This single-center retrospective observational study included 22 tall children treated with low-dose sex steroids. Patients with familial tall stature, constitutional advance of growth or Marfan syndrome were included. Anthropometric measurements at the commencement of treatment, six-monthly intervals on treatment, cessation of treatment, and at final assessment, were evaluated. Bone age (BA) determination, and adult height predictions (PAH) were made using both the tables of Bayley-Pinneau (BP) and Tanner Whitehouse (TW) mark II methods.

**Results:** The final height was significantly lower than the predicted height in girls whereas it was not significantly lower than predicted height in boys. In patients with Marfan syndrome, the final height was only lower than the prediction of TW rather than BP. Non-Marfan cases had significantly lower final height than both the predicted heights. Conversely, although there was a decrease in height SDS over time, this difference was not statistically significant in the study cohort. Starting treatment at early BA (<10 years) did not affect the last height SDS or the difference between predicted height and final height.

**Conclusion:** Sex difference, sex steroid dosage, differences in treatment duration and differences in BA measurement method, PAH method, BA and chronological age at the start of treatment may all influence the therapy response. Shortcomings about these influences can be overcome in future prospective studies with a larger sample size.

## Introduction

Tall stature is defined as a height more than two Standard deviations (SD) above the mean for age, i.e. greater than the 97th percentile for sex and age [1-5]. A child can also be defined tall in relation to his/her midparental height (MPH) if his/her height exceeds more than 2 SD above the MPH (height SD-MPH SD >2.0) [1,5]. The majority of patients presenting with tall stature have a diagnosis of familial tall stature or constitutional advanced growth, which is a diagnosis by exclusion. Some patients with overgrowth may have an underlying endocrine disorder, such as GH/IGF1 excess, precocious exposure to sex steroids, thyrotoxicosis, and obesity, all of which may be associated with an increase in growth velocity. Furthermore, it is also important to note that many genetic syndromes (Sotos, Weaver, Fragile X, Simpson-Golabi-Behmel, Marfan, Klinefelter, Beckwith-Wiedeman Syndrome etc) may be associated with overgrowth [1]. Referrals to a pediatric endocrinologist for an assessment of a child with tall stature are much less frequent than for short stature. This is because tall stature has a wider social acceptance. However, tall stature can also cause psychological problems in children or adolescents, and parents and children will therefore seek out treatments to restrict growth if their predicted adult height (PAH) is thought to be unacceptable. Generally, tall stature does not require any treatment except when it is pathological in origin [1]. To date, no evidence-based guideline has been created with respect to the selection of potential candidates for adult height reduction. Additionally, there is no optimal method for accurately predicting adult height in tall children. The available methods to predict adult height are the Bayley-Pinneau method that usually overestimates adult height, especially when the bone age is less than 9 years, and theTanner-White house Mark 1 and 2 that overestimates adult height when the bone age is less than 9 years, but understimates it when the bone age is more advanced [5-7]. It is estimated that the prediction error is around 3 cm in boys and 2 cm in girls [8]. However, treatment is generally only considered for adolescents with predicted adult heights more than 2.5 SD above the population mean. The most accepted and effective treatment to limit final height is early pubertal induction leading to complete fusion of the epiphyses with earlier achievement of final height, using testosterone in males and estrogens in females [5,9-11]. High doses of estradiol or testosterone have been used to limit final height prognosis by inducing epiphyseal closure. However, high doses of sex steroids are not without short and long-term consequences [1-5,12-15], and are no longer used for limitation of final height. Here, we present the clinical features of a cohort of patients who underwent early pubertal induction with lower doses of testosterone and estrogen in an attempt to limit their final height.

## Material and Methods

### Participants

We performed a retrospective data collection from a medical chart review of patients with tall stature followed up and treated in the pediatric endocrinology clinic at Great Ormond Street Hospital, London, United Kingdom. Clinical diagnosis of tall stature was based on a height more than two standard deviations (SD) above the mean for age, i.e. greater than the 97th percentile for age and sex [1-5]. A detailed history including age at presentation, main clinical features, and the presence of comorbid conditions were recorded for each patient. A clinical examination consisting of anthropometry, assessment of pubertal stage, or dysmorphic features were evaluated for each patient. Only patients with familial tall stature, constitutional advance of growth or Marfan Syndrome were included in the study. This study excluded patients with other syndromic or endocrine disorders associated with tall stature (Sotos, Weaver, Fragile X, Simpson-Golabi-Behmel, Klinefelter, Beckwith-Wiedeman Syndrome, GH/IGF-1 excess, McCune –Albright Sydrome, Homocystinuria), as well as patients with missing data, who were lost to clinical follow-up and patients whose final height was unknown. Moreover, patients who did not start treatment for tall stature were not considered suitable for inclusion in the study because they mostly gave up on continuing follow-up, and did not have homogeneous data for comparison (only a few hospital admissions at different ages).

### Clinical and Radiological Asessment

Follow-up visits, carried out every 6 months during the study period, included measurement of weight (while wearing underwear using a standard calibrated scale), height (using a commercial Harpenden-Holtain stadiometer), body mass index (BMI) and evaluation of pubertal stage according to the criteria of Marshall and Tanner. Age at first evaluation, age at treatment commencement and treatment cessation, height, weight and BMI Standard deviation scores (SDS), growth velocity SDS, and mid-parental height SDS were also utilized in the

study. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m$^2$). The height, weight, and BMI SDS were calculated according to World Health Organization growth data [16]. For statistical analysis, comparisons were made using 4 main anthropometric measurements (at initial evaluation, treatment commencement, treatment cessation, and final assesment). To determine whether there was a change in height SDS with treatment, the changes in anthropometric measurements in SDS over time were calculated. X-ray of the left hand was used for bone age (BA) determination which is important to predict adult height. BA was assessed independently by two different observers (radiologist and a pediatric endocrinologist) according to theTanner Whitehouse 2 method (TW2). Adult height was predicted by both the tables of Bayley-Pinneau (BP) and Tanner Whitehouse mark II methods [17,18]. The final heights of the patients were compared with two adult height prediction methods and the estimated decrease in final height was calculated according to the prediction. The bone age limit for starting treatment earlier was determined as 10 years old and comparisons were also made accordingly.

**Treatment Protocol**

Oral ethinylestradiol (EE2) in girls and an intramuscular injection of a mixture of Testosterone esters in boys (Sustenon 250 mg/ml; 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate) were used. EE2 was started at a dose of 2 µg daily and increased at 3-6 monthly intervals to reach a dose of 15 - 20 µg over a mean treatment period of 6.7±1.0 years. In cases where girls needed therapy for more than 2.5 years, or where menstrual bleeds occurred, a progestagen was added to the treatment (natural micronized progesterone 200 mg and synthetic progesterone medroxyprogesterone acetate 5 mg once daily in 12–14 day blocks every month). In boys, an intramuscular injection of testosterone esters was commenced at a dose of 50 mg monthly, increasing to a dose of 150 mg two weekly over a mean treatment duration of 9.4±1.2 years. Before commencing treatment, any underlying pathology was excluded. BA at the cessation of the sex hormone therapy was estimated to be less than approximately 17 years in boys and 15 years in girls, indicating that approximately 98.8% and 99.3% of the final adult height had been achieved in boys and girls, respectively [7].

**Statistical Analysis**

The data were analyzed using SPSS software (Statistical Package for the Social Sciences, version 21; SPSS Inc., Chicago, IL, USA). The results were given as mean±SDS or as percentages, where appropriate. Data were analyzed using descriptive statistical methods (mean, Standard deviation, median, frequency, rate, Minimum, Maximum) as well as some methods for comparing quantitative data. The repeated measures ANOVA was used to compare means across more variables that are based on repeated observations. The Bonferroni correction was performed during the analysis because of the increased risk of a type I error. The Greenhouse-Geisser is used to assess the change in a continuous outcome with three or more observations across time or within-subjects against violations of sphericity. The Wilcoxon signed rank test, was also used to determine whether the mean difference between two sets of observations when each subject or entity was measured only twice.

**Results**

**Baseline Characteristics**

The files of 26 patients who received treatment for tall stature were examined. Four patients who had a diagnosis of familial tall stature, were not included in the study because of incomplete data and follow-up. Data were extracted on a total of 22 patients treated with tall stature in this study; 81.8% of the patients (n = 18) were female and 18.2% (n = 4) were male. Of the cohort, 22.7% (n=5) had Marfan Syndrome (3F, 2M) whereas the rest (77.3%, n=17) had familial tall stature or constitutional growth advance. The mean age of patients at initial evaluation was 7.6±1.9 years, with a mean BA of 9.8±1.7 years. Oral EE2 treatment was started at 9.6±1.4 years in girls, whilst testosterone was commenced at 11.3±1.5 years in boys. In patients with Marfan syndrome, the median age for starting pubertal induction was 9.8 years (min: 7.5 and max:11.2). There were a few patients whose treatment started after bone age 12 (n=3 male [2 Marfan Syndrome 1 constitutional advance of growth], n=1 female). There was only one Marfan syndrome patient with BA<10 years when treatment commenced. The

mean age of treatment cessation was 13.0±1.4 years in girls and 14.8±1.9 years in boys respectively. Patients were followed up for 1.6±1.0 years after discontinuation of treatment.

**Effect on height**

The changes in anthropometric measurements in SDS over time were shown in Table 1. Although there was a decrease in height SDS over time, this difference was not statistically significant in the study cohort (Table 1). The reduction in height SDS over time throughout treatment and follow-up of non-Marfan Syndrome patients was not significant whereas the height SDS reduction of Marfan Syndrome patients over time approached significance (p=0.06) (Table 1). The results of the treatment protocol with height predictions according to gender and main diagnosis were also summarized in Tables 2 and 3 respectively. The final height was significantly lower than the predicted height in girls; however the final height was not significantly lower than the predicted height in boys. In patients with Marfan syndrome, final height was only lower than the TW2 prediction, in contrast to the BP prediction. Non-Marfan syndrome patients achieved a significantly lower final height than both TW2 and BP predicted heights (Table 3).

The mean final height of girls was significantly higher than MPH (p=0.04). Only five girls (27%) achieved a final height that was lower than the MPH. All 4 boys achieved a final height that was greater than the MPH, but this did not reach statistical significance (p=0.07). Patients with Marfan Sydrome reached final heights that were similar to their MPH (p=0.13). However, patients with familial tall stature or constitutional advanced growth achieved final heights that were significantly greater than the MPH (p=0.01) (Table 3). Commencement of treatment at earlier bone ages (<10 years) did not affect the final height SDS or the difference between predicted height and final height; moreover this was similar in both genders (Table 4).

**Side effects**

None of the patients manifested side effects related to either testosterone (aggressive behaviour, painful erections, severe forms of acne) or estrogen (weight increase, headache, hypertension, increased risk of thromboembolic events) therapy during the follow-up period.

**Discussion**

This is one of a few studies to have evaluated the effect of sex steroid therapy on final height in patients with tall stature. In addition, the articles on this subject mostly describe the use of high-dose sex steroids and are older publications. This issue has not been addressed more recently. This study is important as it describes the long-term use of lower doses of sex steroid.We have documented the results of sex steroid treatment not only in patients with familial tall stature and constitutional advanced growth, but also in a small subgroup of patients with Marfan Syndrome. Most of the articles compare final height and predicted height, rather than detailing the height SDS trajectory over time. The current study obtained long-term data of patients from initial evaluation to achievement of final height, allowing an assessment of height SDS changes over time. To date, sex steroids remain the most studied and widely used off-label treatment to restrict growth [19]. However, the use of sex steroid therapy in tall stature is still controversial, and its benefits remain unproven.

High doses of estrogen or testosterone (in girls, 100-500 μg/day EE2 and in boys testosterone ester mixtures [testosterone propionate, fenylpropionate, isohexanoate, and decanoate] 250 mg given every week or every 2 weeks) have been used to limit final height by inducing epiphyseal closure in the past [1,7,19-25]. In girls, EE2 given orally, and combined with cyclical progestagen where menstrual bleeding has commenced, has previously been shown to reduce the final height by between 2.1 and 10 cm [7,17]. In boys, the administration of testosterone 250-1000 mg monthly has shown similar results, with a reduction in final height of 4.7-9.6 cm. Testosterone enanthate doses have been reported to demonstrate a similar efficacy on final height using 50% of the doses.[7,12]. Short-term high-dose testosterone therapy in boys with tall stature has also shown to be as effective as long-term therapy [21]. However, high doses of sex steroids are no longer recommended to restrict growth due to their short-and long-term consequences [1]. Treatment of constitutionally tall girls with low doses of oestrogens has been reported to be equally effective in reducing the final height as the usually administered high doses [22,26]. The lowest effective and safest therapeutic dose is still a matter of scientific debate. We have summarized different treatment regimens reported previously in boys and girls in Table 5. Recently,

induction of puberty with very low doses has also been reported to be effective and the most accepted treatment to restrict adult height in girls (starting with doses 2 μg oral EE2 and increasing gradually to 15 μg daily) [1]. In our study, we used these more physiological dose regimens of sex steroids with the aim of achieving less suppression of gonadotropins as recently recommended [1]. Thus, to the best of our knowledge, our study reports the use of the lowest doses reported to date in the literature. However, our study showed that height SDS over time did not change statistically with this treatment. On the other hand, our study reports that the final height was significantly lower than the predicted height in girls whereas the final height was not significantly lower then predicted height in boys. This raises some interesting questions. The pubertal growth spurt has long been considered to be an androgen-dependent process. However, there is abundant clinical and experimental evidence showing that estrogens may be primarily responsible for accelerated growth during puberty [8]. Furthermore, high dose testosterone in boys is shown to be less effective than estrogenic treatment in girls due to the bone age at the start point of treatment [5]. This raises the possibility that estrogen treatment used at more physiological doses may be more effective than testosterone treatment in the management of tall stature. While all these questions may sound believable, it should be kept in mind that the small number of male patients in our study may also lead to these results, and larger future studies are needed to shed light on these questions. Additionally, one needs to consider whether adult height predictions are equally reliable in both genders. Estimation of PAH is one factor that is taken into account when deciding whether or not height-reducing treatment is advisable for a child with tall stature. Furthermore, final height compared with PAH before commencement of height-reducing treatment is a frequently used method to evaluate the effect of treatment. However, the risk of error inherent in height-prediction methods is well known, and studies have shown both underestimation and overestimation of final adult height depending on the method used [7,13]. Traditional PAH models relying on manual bone age readings have high interobserver variability and individual variations in height prediction have also been shown to occur. However, the methods of height prediction have found to be clinically acceptable in tall stature girls [7,13]. Nevertheless, our study results showed that these two traditional PAH methods did not give completely overlapping results, but both methods overestimated the final height in girls. Moreover, major differences in height reduction were observed depending on the height prediction method which was employed in both genders. Anciently, the estimated confidence limits of PAH determined as large (+/- 8 cm) for the two methods up to a bone age of 15 years [6]. In literature, Tanner-Whitehouse mark II gives a better estimation of final height up to the bone age of 13 years and 9-12 years respectively in tall boys and girls whereas the overestimation of final height is higher in older bone ages [6]. On the other hand, up to the bone age of 12-14 years the final height is massively overestimate by the Bayley-Pinneau method in both genders but this method give relatively accurate estimations thereafter [6]. Thus, there is no best or most accurate method for PAH in tall children, first choice method may be differ with respect to sex and bone age [6]. Our study group included only a few patients whose treatment started after bone age 12. More than half of the patients, treatment began before bone age was 10. At the beginning of treatment, PAH were calculated higher in both genders with Tanner-Whitehouse Mark II. The amount of reduction in final height also differed according to the two PAH methods. The fact that these PAH methods give different confidence limits for different bone ages and most of our patients had younger bone age than 10 years might cause these differences to be evident in our study. From this point of view, more objective and more reliable PAH methods are still needed and recently the incorporation of artificial intelligence has improved the accuracy of bone age readings and their incorporation into predicting adult height models models [27]. Thus, our results based on the comparison of final height and PAH in both sexes should be supported by future larger cohort studies which also include more reliable PAH methods to clarify the effect of more physiological estrogen and testosterone therapy in the management of tall stature.

Previous studies have shown an association between height reduction and BA at the commencement of EE2. The greatest effect on height reduction was observed when EE2 treatment was initiated at a younger BA [15]. Moreover, in boys, treatment commencement at BAs older than 14-15 yr, depending on the method of BA assessment, was not recommended, because androgen administration caused additional growth instead of growth inhibition. It is recommended that referral should take place early, preferably before puberty, and treatment should not be discontinued before complete closure of the epiphyses of the hand and wrist occurred to avoid significant post-treatment growth [9]. For optimal results, these therapeutic agents should be started at

a younger BA [7,28,29]. However, in the current study, starting treatment at an earlier bone age did not affect the final height SDS or the difference between predicted height and final height.
Experience with sex steroids for height reduction in Marfan Syndrome is limited [30,31]. Estrogen treatment in Marfan Syndrome has been more studied than testosterone treatment in this syndrome [30,31]. Marfan patients treated with sex steroids have been reported to have similar treatment effects as constitutional advanced growth [32]. Although the types and doses of estrogens vary in the literature, 50-300 μg of EE2 per day is commonly used for height modification in girls with Marfan Syndrome [30]. Recently, Estradiol valerate, which is more physiologic than EE2, has been used in patients with Marfan Syndrome [30,33]. Initiating treatment with estradiol valerate before the age of 10.5 years has been reported to be effective in female patients with Marfan Syndrome [30,33]. Our study included only 5 patients with Marfan Syndrome, and only one patient with an age>10.5 years at initiation of treatment. More physiologic, lower doses of EE2 were used in Marfan Syndrome patients as was the case with constitutional tall stature in this study. We demonstrated that the height SDS of patients with Marfan Sydrome overtime decreased with sex steroid treatment, but this did not achieve statistical significance. Patients with Marfan Sydrome reached a final height similar to their MPH in the current study. However, comparison with parental target height in Marfan Syndrome also has limitations. Clearly, an affected parent with this autosomal dominant condition will compound the tall stature. Additionally, the genetic contribution to adult height from tall unaffected parents is unclear [30]. On the other hand, in the current study, the final height of patients with Marfan Syndrome was only lower than the TW2, in contrast to the BP, prediction. One of the methodological difficulties of evaluating height-limiting therapies in children with Marfan Syndrome is that the height prediction models designed for the “normal” population, based on skeletal age, such as Tanner Whitehouse and Bayley–Pinneau, may have limited applications to syndromic tall stature.
Currently, high dose sex steroids are no longer widely recommended to limit growth due to their short and long-term consequences (myalgia, acne, gynecomastia, aggressive behavior, trouble some erections, weight gain, decrease semen quality in males; weight gain, night cramps, galactorrhea, ovarian cysts, predisposition to thrombosis, increase risk of breast tumours, malignant gynaecological tumours, malignant melanoma and premature ovarian failure in females) [8,16,28,34,35]. In the current study, no adverse effects were detected during the short and long-term follow-up. However, data on future infertility or cancer risks could not be included in the study, since we followed the patients for only a few years after treatment discontinuation.
Other therapies such as a nocturnal infusion of octreotide, a somatostatin analogue (201-995), or surgical closure of the epiphyses or percutaneous epiphysiodesis procedures have been considered to reduce final height in tall children [1,36]. Today, surgical treatment with percutaneous epiphysiodesis is also preferred for patients with a bone age less than 12.5 years in girls and 14 years in boys [37]. However, treatments other than sex hormones were not included in this study. Recently, it has been demonstrated that a selective estrogen receptor (ERα) agonist has the capacity to suppress longitudinal bone growth in treated mice [38]. This may have direct implications for the development of a specific treatment for extreme tall stature as a future treatment approach.

**Limitations of the current study**

Our study has several limitations. First, the nature of the study was a retrospective review of medical records from a single center. Secondly, the lack of statistical significance may be due to the small sample size. Another limitation of our study is that patients who did not receive treatment were not included in the study and comparison results could not be presented. In addition, manually determined BA is subject to both inter- and intra-observer variability. These shortcomings can be overcome in future prospective studies with a larger sample size, and with the use of automated bone age evaluation using software such as Bone Xpert. However, our patients were recruited over 7.2±1.9 years, demonstrating the rarity of patients seeking treatment to limit their final height. Males are generally happy to achieve tall stature, hence the reduced number of males in this study. Importantly, tall stature is now perceived to be acceptable, and perhaps even desirable, in women. Hence, it is likely that the number of individuals seeking height-limiting therapies will dwindle further. Additionally, late negative effects on fertility or the development of estrogen-induced tumours such as breast or uterine malignancies could not be addressed in this study. The main indication for height limiting therapies may be in girls with conditions such as Marfan Syndrome.

## Conclusion

Currently, the decision on whether to intervene or not with height-limiting therapies in children and adolescents with tall stature is still controversial. There are no evidence-based guidelines available on whether to treat or not and on which medication to use. Nevertheless, there remains a significant degree of uncertainty regarding the efficacy of exogenous sex steroids in limiting final height, whether used as part of a high or lower dose strategy. The lowest effective dose has to be determined in a randomized, prospective clinical trial. Moreover, gender-based differences in efficacy and safety may also determine their acceptability. Lower, possibly more physiological, estrogen doses may be more effective than lower doses of testosterone in the therapy of tall stature. Thus, further studies are required that then need to address gender differences, different sex steroid dosages, differences in treatment duration, and differences in BA and PAH methods of evaluation. The BA and chronological age at the start of treatment may also influence the therapy response.

## Statement of Ethics

Ethical approval and consent were not required as this study was based on publicly available data

## Conflict of Interest Statement

The authors have no conflicts of interest to declare


## Funding Sources

The authors did not receive any funding.


## Author Contributions

All authors participated in the interpretation and analysis of the study data, and in the drafting, critical revision, and approval of the final version of the manuscript. Akcan N, Verdecchia F, Hindmarsh P, Dattani M conceived and designed the study. Akcan N and Verdecchia F collected the data and conducted statistical analyses. Hindmarsh P, and Dattani M were the medical monitors.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## References


1. Corredor B, Dattani M, Gertosio C, Bozzola M. Tall Stature: A Challenge for Clinicians. Curr Pediatr Rev. 2019;15(1):10-21. doi:10.2174/1573396314666181105092917.
2. Sada V, Puliani G, Feola T, Pirchio R, Pofi R, Sesti F, et al. Tall stature and gigantism in transition age: clinical and genetic aspects-a literature review and recommendations. J Endocrinol Invest. 2024;47(4):777-793. doi: 10.1007/s40618-023-02223-z.
3. Urakami T. Tall stature in children and adolescents. Minerva Pediatr. 2020;72(6):472-483. doi: 10.23736/S0026-4946.20.05971-X.
4. Davies JH, Cheetham T. Investigation and management of tall stature. Arch Dis Child. 2014; 99: 772-7.
5. Meazza C, Gertosio C, Giacchero R, Pagani S, Bozzola M. Tall stature: a difficult diagnosis? Ital J Pediatr. 2017;43:66. doi: 10.1186/s13052-017-0385-5.
6. Joss EE, Temperli R, Mullis PE. Adult height in constitutionally tall stature: Accuracy of five different height prediction methods. Arch Dis Child. 1992;67:1357-62.
7. DeWaal WJ, Greyn-Fokker MH, Stijnen T,van Gurp EA, Toolens AM, de MunickKeizer-Schrama SM, et al. Accuracy of final height prediction and effect of growth-reductive therapy in 362 constitutionally tall children. J Clin Endocrinol Metab. 1996;81:1206-16.
8. Drop SL, De Waal WJ, De Muinck Keizer-Schrama SM. Sex steroid treatment of constitutionally tall stature. Endocr Rev. 1998;19(5):540-58. doi: 10.1210/edrv.19.5.0345.
9. Matthews D, Bath L, Hogler W, Mason A, Smyth A, Skae M. Hormone supplementation for pubertal induction in girls. Arch Dis Child. 2017;102(10): 975-80.

10. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015 Sep;11(9):547-64. doi: 10.1038/nrendo.2015.112.
11. Howard S, Dunkel L. Sex Steroid and Gonadotropin Treatment in Male Delayed Puberty. Endocr Dev. 2016;29:185-97. doi: 10.1159/000438891.
12. Reinehr T, Gueldensupp M, Wunsch R, Bramswig JH. Treatment of tall stature in boys: Comparison of two different treatment regimens. Horm Res Paediatr. 2011;76:343-347. doi:10.1159/000332735.
13. Upners EN, Juul A. Evaluation and phenotypic characteristics of 293 Danish girls with tall stature: effects of oral administration of natural 17β-estradiol. Pediatr Res. 2016;80(5):693-701. doi: 10.1038/pr.2016.128.
14. DeWaal W, Torn M, de MuinckKeizer-Schrama S, Aarsen R,Drop S. Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. Arch Dis in Childhood. 1995;73(4): 311-5.
15. Hendriks AE, Boellaard WP, van Casteren NJ, Romijn JC, de Jong FH, Boot AM et al. Fatherhood in tall men treated with high-dose sex steroids during adolescence. J Clin Endocrinol Metab. 2010;95(12):5233-40. doi: 10.1210/jc.2010-0435.
16. WHO multicentre growth reference study group. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass indexfor-age: methods and development. Geneva: World Health Organization; 2006.
17. Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healy MJ, Goldstein H, editors. Assessment of Skeletal Maturity and Prediction of Adult Height (TW2 Method). 2nd ed. London: Academic Press; 1975.
18. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr. 1952;40(4):423-41. doi: 10.1016/s0022-3476(52)80205-7.
19. Albuquerque EVA, Scalco RC, Jorge AAL. Management of Endocrine Disease: Diagnostic and therapeutic approach of tall stature. Eur J Endocrinol. 2017;176(6):R339-R353. doi: 10.1530/EJE-16-1054.
20. De Waal WJ, Vreeburg JT, Bekkering F, de Jong FH, de Muinck Keizer-Schrama SM, Drop SL et al. High dose testosterone therapy for reduction of final height in constitutionally tall boys: Does it influence testicular function in adulthood? Clinical Endocrinology. 1995;43:87–95. doi:10.1111/j.1365-2265.1995.tb01897.x.
21. Brämswig JH, von Lengerke HJ, Schmidt H, Schellong G. The results of short-term (6 months) high-dose testosterone treatment on bone age and adult height in boys of excessively tall stature. Eur J Pediatr. 1988;148(2):104-6. doi: 10.1007/BF00445913.
22. Normann EK, Trygstad O, Larsen S, Dahl-Jørgensen K. Height reduction in 539 tall girls treated with three different dosages of ethinyloestradiol. Archives of Disease in Childhood.1991;66:1275–1278. doi:10.1136/adc.66.11.1275.
23. Sorgo W, Scholler K, Heinze F, Heinze E, Teller WM. Critical analysis of height reduction in oestrogen-treated tall girls. Eur J Pediatr. 1984;142(4):260-5. doi: 10.1007/BF00540248.
24. Binder G, Grauer ML, Wehner AV, Wehner F, Ranke MB. Outcome in Tall Stature. Final Height and Psychological Aspects in 220 Patients with and without Treatment. Eur J Pediatr.1997;156 (12):905–10. Doi.10.1007/s004310050740.
25. Venn A, Hosmer T, Hosmer D, Bruinsma F, Jones P, Lumley J, et al. Oestrogen treatment for tall stature in girls: estimating the effect on height and the error in height prediction. Clin Endocrinol (Oxf). 2008;68(6):926-9. doi: 10.1111/j.1365-2265.2007.03128.x.
26. Grüters A, Heidemann P, Schlüter H, Stubbe P, Weber B, Helge H. Effect of different oestrogen doses on final height reduction in girls with constitutional tall stature. Eur J Pediatr. 1989;149(1):11-3. doi: 10.1007/BF02024324.
27. Chávez-Vázquez AG, Klünder-Klünder M, Garibay-Nieto NG, López-González D, Sánchez-Curiel Loyo M, Miranda-Lora AL. Evaluation of height prediction models: from traditional methods to artificial intelligence. Pediatr Res. 2024 Jan;95(1):308-315. doi: 10.1038/s41390-023-02821-w.
28. Weimann E, Bergmann S, Böhles HJ. Oestrogen treatment of constitutional tall stature: a risk-benefit ratio. Arch Dis Child 1998;78:148–151

29. Joss EE, Zeuner J, Zurbrügg RP, Mullis PE. Impact of different doses of ethinyl oestradiol on reduction of final height in constitutionally tall girls. Eur J Pediatr. 1994;153(11):797-801. doi: 10.1007/BF01972886.
30. Lee DY, Hyun HS, Huh R, Jin DK, Kim DK, Yoon BK, et al. Estrogen-mediated height control in girls with Marfan Syndrome. J Korean Med Sci. 2016;31(2):275-9. doi: 10.3346/jkms.2016.31.2.275.
31. Ucar SK, Paterson WF, Donaldson MD, Young D. Ethinyl estradiol treatment for growth limitation in girls with Marfan's syndrome-experience from a single center. Endocr Res. 2009;34(4):109-20. doi: 10.3109/07435800903207283.
32. Rozendaal L, le Cessie S, Wit JM, Hennekam RC, The Dutch Marfan Working Group. Growth-reductive therapy in children with Marfan Syndrome. J Pediatr. 2005;147(5):674-9. doi: 10.1016/j.jpeds.2005.06.011. PMID: 16291362.
33. Kim SE, Lee DY, Kim MS, Cho SY, Jin DK, Choi D. Appropriate age for height control treatment in patients with Marfan Syndrome. Front Endocrinol [Lausanne]. 2021;12:708931. doi: 10.3389/fendo.2021.708931.
34. Benyi E, Kieler H, Linder M, Ritzén M, Carlstedt-Duke J, Tuvemo T, 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.
35. Hannema SE, Sävendahl L. The Evaluation and management of tall stature. Horm Res Paediatr. 2016;85(5):347-52. doi: 10.1159/000443685.
36. Benyi E, Berner M, Bjernekull I, Boman A, Chrysis D, Nilsson O, et al. Efficacy and safety of percutaneous epiphysiodesis operation around the knee to reduce adult height in extremely tall adolescent girls and boys. International Journal of Pediatric Endocrinology 2010;2010:740629. doi: 10.1155/2010/740629
37. Hansen AB, Wøjdemann D, Renault CH, Pedersen AT, Main KM, Raket LL, et al. Diagnosis of endocrine disease: Sex steroid action in adolescence: too much, too little; too early, too late. Eur J Endocrinol. 2021;184(1):R17-R28. doi: 10.1530/EJE-20-0545.
38. Iravani M, Lagerquist M, Ohlsson C, Sävendahl L. Regulation of bone growth via ligand-specific activation of estrogen receptor alpha. J Endocrinol. 2017;232(3):403-410. doi: 10.1530/JOE-16-0263. Epub 2016 Dec 20. PMID: 27999091.

Table 1. Antropometric parameters of cases during follow-up

| | On Admission | At commencement of treatment | Cessation of treatment | Last Assessment | |
|---|---|---|---|---|---|
| | | Mean±sd | | | *p* value |
| **Total n=22 (f=18, m=4)** | | | | | |
| Age (years) | 7.6±1.9 | 9.9±1.5 | 13.3±1.6 | 14.7±1.4 | |
| H (cm) | 141.9±11.9 | 157.8±9.2 | 177.8±8.7 | 181.4±9.4 | |
| W (kg) | 35.5±11.3 | 40.1±20.7 | 63.7±15.0 | 79.7±37.2 | |
| BMI | 17.3±3.9 | 18.5±4.4 | 20.0±4.0 | 20.5±4.4 | |
| H SDS | 3.5±1.1 | 3.4 ± 1.3 | 3.4 ± 1.1 | 3.1 ± 1.0 | 0.4 |
| W SDS | 1.8±1.2 | 1.5 ± 1.2 | 1.6 ± 1.0 | 1.4 ± 1.2 | **0.02*** |
| BMI SDS | 0.3±1.5 | 0.3 ± 1.5 | 0.2 ± 1.3 | 0.8 ± 1.3 | 0.1 |
| **Non-Marfan (n=17)** | | | | | |
| H SDS | 3.1±0.9 | 3.0±1.0 | 3.0±0.9 | 2.9±0.9 | 0.78 |
| W SDS | 1.7±1.2 | 1.5 ± 1.2 | 1.6 ±1.1 | 1.4 ± 1.2 | 0.09 |
| BMI SDS | 0.4±1.5 | 0.4 ± 1.5 | 0.3 ± 1.4 | 0.1 ± 1.4 | 0.13 |
| **Marfan (n=5)** | | | | | |
| H SDS | 4.6±1.0 | 4.6±1.2 | 4.3±1.4 | 3.6±1.3 | 0.06 |
| W SDS | 2.0±1 | 1.8±1.1 | 1.7±1.0 | 1.5±1.3 | 0.13 |
| BMI SDS | -0.09±1.3 | 0.03±1.5 | -0.1±1.2 | -0.08±1.2 | 0.95 |

*BMI: body mass index, H: Height, f:female, m:male, W:weight*
**statisticallysignificant*

Table 2. Comparison of Predicted and Final Height

| | MPH (cm) | Predicted height (cm) | Predicted height (cm) | Height at followup (cm) | | Comparison of Predicted and Final Height | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sex (n)** | | **TW** | **BP** | **Cessation of therapy** | **FH** | ***p* value** | | **Height reduction (cm)** | |
| | | | | | | **TW-FH** | **BP-FH** | **TW-FH** | **BP-FH** |
| **F (18)** | 175±5.0 | 198.9±9.8 | 183.5±4.4 | 174.4±4.0 | 177.5±3.7 | **0.00*** | **0.00*** | 21.5±8.4 | 5.3±4.8 |
| **M (4)** | 187.9±4.8 | 210.5±9.8 | 201.8±3.8 | 193.2±7.7 | 198.9±6.6 | 0.07 | 0.27 | 12.3±10.3 | 3.6±6.2 |

BP: Bayley-Pinneau, F: Female, FH: Final Height, M: Male, MPH: Midparental Height, TW: Tanner Whitehouse mark II
*Wilcoxon Signed Rank Test, *statisticallysignificant*

Table 3. Comparison of Predicted and Final Height in Marfan and Non-Marfan Cases

| | MPH (cm) | Predicted height (cm) | Predicted height (cm) | Height at followup | | Comparison of FH and MPH | Comparison of Predicted and Final Height | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Diagnosis (n)** | | **TW** | **BP** | **Cessation of therapy** | **FH** | ***p* value** | ***p* value** | | **Height reduction** | |
| | | | | | | | **TW-FH** | **BP-FH** | **TW-FH** | **BP-FH** |
| **Marfan (5)** | 179.4±6.1 | 202.6±8.9 | 193.9±12.5 | 181.4±14.6 | 188.3±15 | **0.13** | **0.04*** | **0.46** | 13.8±8.9 | 0.44±3.3 |
| **CAG (17)** | 176.8±7.4 | 200.7±11.3 | 185.4±6.7 | 176.8±6.5 | 179.4±6.4 | **0.01*** | **0.00*** | **0.00*** | 21.6±8.8 | 6.4±4.5 |

*CAG:*constitutional advanced growth,FH: Final Height, MPH: Midparental Height, TW: Tanner Whitehouse mark II
*Wilcoxon Signed Rank Test, *statisticallysignificant*

Table 4. Comparison of Predicted and Final Height dueto Bone Age BeforeTherapy

| | | Bone Age before therapy (years) | | *p* value |
|---|---|---|---|---|
| | | <10 | 10≤ | |
| N | | 14 | 8 | |
| Final Height SDS | | 3±0.3 | 3.3±0.4 | 0.76 |
| Difference between Predicted Height and Final Height | TW-FH | 22.5±2.3 | 15.3±3.1 | 0.08 |
| | BP-FH | 6.0±1.4 | 3.3±1.6 | 0.28 |

*Mann Whitney U Test*

Table5. Literature data summarizing the effect of hormonal treatment in children with tall stature

| Reference | Study sample | Dosage of therapy | Result of study |
|---|---|---|---|
| Sorgo W et al. 1984 [18] | 14 F | • 10 F: 0.3 mg EE2 daily and 5 mg lynestrenol from day 18-24 of the cycle.<br>• 4 F: 7.5 mg conjugated estrogens per day with the same dose of the progestagen | GR: 2.3-6.5 cm |
| Grüters A et al. 1989 [21] | 82 F | • 100 µg/day EE2 ( n=44)<br>• 300-500 µg/day EE2 ( n=38) | • The dose of EE2 had no effect on FH reduction [high dose group: 4.9 +/- 2.6 cm, low dose group: 5.1 +/- 2.4 cm. |
| Normann EK et al.1991 [17] | 539 F | • 100 µg/day EE2 ( n=98)<br>• 250 µg/day EE2 ( n=178)<br>• 500 µg/day EE2 ( n=263) | • No difference between groups<br>• 100 µg/day EE2 for about 20 months is sufficient to reduce FH |
| Joss EE et al. 1992 [4] | 73 F<br>(52 treated, 21untreated) | • 100 µg/day EE2 ( n=11)<br>• 300 µg/day EE2 ( n=25)<br>• 500 µg/day EE2 ( n=16) | • Using TW II, EE2 treatment reduced FH compared with the untreated girls in a weak dose-dependent manner, 2.3 cm [100 µg/day], 3.0 cm [300 µg/day], and 3.8 cm [500 µg/day].<br>• Dose dependency was not found on applying the Bayley-Pineau method<br>• [100 µg/day; 4.1 cm;<br>• 300 µg/day: 4.2 cm;<br>• 500 µg/day: 4.5 cm]. |
| DewaalWJ et al. 1996 [5] | 143 untreated (55 M, 88 F)<br>249 treated with high doses of sex hormones (60 M, 159 F) | • testosterone ester mixtures [Sustanon; Organon, Oss, Netherlands; testosteronepropionate, fenylpropionate, isohexanoate, anddecanoate; 250 mg every week (n = 45), 250 mg every 2 weeks (n = 4), or 500 mg every 2 weeks (n = 3)].<br>• an oral testosterone ester [Andriol, Organon; testosteroneundecanoate; 240-320 mg/day] (n=4)<br>• a single testosterone ester [Neohombreol, Organon; testosteronepropionate; 25-30 mg/day] for 6-30 months (n=4)<br>• 200 µg EE2/hay, orally(n=143)<br>• 300 µg EE2/day(n=3) | • GR varied from -0.5[2.4] to 0.3 [1.4] cm in boys; from-0.6 [2.1] to 2.4 [1.4] cm in girls.<br>• The FH reduction was dependent on the BA at start of therapy and was more pronounced at a younger BA.<br>• In boys, the treatment effect was significantly negative at BAs exceeding 14-15 yr. |

| | | | |
|---|---|---|---|
| | | • 100 µg EE2/day(n=3) | |
| Binder G et al 1997 [19] | 135 F, 85 M | • Orally 7.5 mg/day conjugated estrogens in F [plus 5 mg dydrogesterone for 10 days a month]<br>• 500 mg testosteroneenantate, intramuscularly, every 2 weeks in M. | • FH reduction: 4.4 cm<br>• The mean of GR: 3.6 cm [range: 11.9 cm to -3.3 cm] in F and 4.4 cm [range: 14.2 cm to -5.2 cm] in M.<br>• More effective when started at an earlier chronological and BA |
| Weinmann Eet al. 1998 [22] | 50 F | • Conjugated estrogens [7.5–11.25 mg/day] | • FH was 5.2 [3.3] cm less than the predicted height. |
| Venn et al. 2008 [20] | 279 F | • Until 1971, DES at 3 mg daily.<br>• After 1971, EE2 at a dose of 150 µg daily, starting at 50 µg/day in the first week and progressing to 100 µg/day in the second week.<br>• Norethisterone, 5 mg twice daily for 4 days at monthly intervals<br>• Treatment duration: 2 years | • GR: 2.5 cm<br>• Effect decreased by 1cm per year of delay in treatment start |
| Reinehr T et al. 2011 [10] | 161 M | • Testosteroneenanthate 500 mg in 114 M and 250 mg in 47 M, intramuscularly every 2 weeks | • 250 mg testosteroneenanthate in every 2 weeks was as effective in GR as a dose of 500 mg every 2 weeks. |
| Benyi E et al. 2014 [28] | 172 treated<br>197 untreated F | • EE2 500µg [250 – 1,000] Daily | • Median predicted FHs at time of assessment differed by 2.7 cm between the two groups (183.9 and 181.2 cm in treated and untreated, respectively)<br>• Median FH was identical in the two groups (181.0 cm) |
| Upners EN et al. 2016 [11] | 207 F;<br>60 (29%) treated with oral E2<br>3 (1%) both oral E2 and surgical epiphysiodesis<br>1 girl (<1%) with surgical epiphysiodesis alone<br>143 (69%) untreated | • Orally17β-estradiol starting doses 0.2to 4 mg . | • FH was reduced with 1.6 ± 2.1 cm |
| Lee DY et al. 2016 [24] | 8 Marfan F | • Estradiol valerate 2 mg/day for 6 months, increased every 2 months by 2 mg/day until the height increment was <1 cm for 2 months. | • Median FH (172.6 cm) was shorter than the median gcPFHt (181.0 cm) and baPFHt (175.9 cm)<br>• Estradiol valerate may be an effective treatment when started under 11 years old |

| | | | |
|---|---|---|---|
| Kim SE et al. 2021 [29] | 17 Marfan F | • Estradiol valerate 2 mg/day for 6 months, increased every 2 months by 2 mg/day and up to a maximum dose of 12 mg/day | • The gcHtD: 10.6 (10.2, 13.5) cm for ≤10.5 years<br>• The gcHtD: 0.6 (−3.65, 5.85) cm for >10.5 years.<br>• The baHtD: 10.1 (7.31, 11.42) cm for ≤10.5 years<br>• The baHtD: 3.83 (0.84, 6.4) cm for >10.5 years. |

BA: bone age, baHtD:height difference between final and predicted, baPFH: projected final height by bone age DES:diethylstilboestrol, EE2:ethinylestradiol, F: female, FH:final height, GR: growth reductions, gcHtD; height difference between final and predicted height by growth curve, gcPFHt: projected final height by growth curve, M: male