INTRODUCTION

The attainment of one's final adult height is a complex interplay of environmental, genetic, familial, nutritional, and hormonal factors. The sexually dimorphic trait of height is one aspect of the experience of transgender and gender-diverse (TGD) individuals that may influence their gender dysphoria and satisfaction with their transition. In this article, we have reviewed the current knowledge of the factors that contribute to one's final adult height and how it might be affected in TGD youth who have not experienced their gonadal puberty in the setting of receiving gonadotropin-releasing hormone analog (GnRHa) and gender-affirming hormonal treatment. Additional research is needed to characterize the influence of growth and final adult height on the lived experience of TGD youth and adults and how to best assess their growth, predict their final adult height, and how medical transition can be potentially modified to help them meet their goals.

FACTORS INFLUENCING LINEAR GROWTH

Prepubertal growth in TGD youth does not differ from their cis-gender peers, as medical intervention, which would alter the sex steroid milieu, is not indicated until the onset of puberty. Prior to pubertal onset, both birth-assigned sexes have similar heights during childhood. Linear growth in childhood and adolescence occurs via the process of endochondral ossification at the cartilaginous epiphyseal plate (“growth plate”), located near the distal ends of the long bones. Regulation of growth is complex and occurs by both paracrine and endocrine mechanisms including involvement of growth hormone (GH), which stimulates production primarily of insulin-like growth factor-1 (IGF-1) from the liver, as well as contributions from thyroid hormone, glucocorticoids, androgens, and sex steroids.
Additionally, paracrine effects from fibroblast growth factors, bone morphogenic proteins, Indian hedgehog, and parathyroid hormone have also been shown to be involved in disorders of short stature and may be influenced by sex steroids.\textsuperscript{5,10-13} Other non-endocrine factors such as genetic disorders, renal disease, pre-natal factors, and malnutrition may also negatively impact growth.\textsuperscript{5} Additionally, height is influenced by sex chromosomes with genes involved in height on both the X and Y chromosome, as supported by sex chromosome aneuploidies, in which an increase in the number of chromosomes, especially the Y chromosome, leads to tall stature.\textsuperscript{14,15}

3 | PUBERTAL GROWTH PATTERNS

Puberty initiation is marked by the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus in a pulsatile fashion.\textsuperscript{16} This secretory pattern is also the target of GnRHa in the management of pediatric gender dysphoria.\textsuperscript{17} Pulsatile GnRH stimulates pituitary-luteinizing hormone (LH) and follicle-stimulating hormone section and this in turn causes downstream activation of the gonads. There is a predominance of production of testosterone by the testes and estrogen from the ovary, which leads to secondary sexual characteristics and the pubertal growth spurt.\textsuperscript{16} Testosterone also increases GH secretion in birth-assigned boys and estrogen increases GH secretion in both assigned sexes.\textsuperscript{18} Birth-assigned boys demonstrate increased GH pulse amplitude and higher cumulative GH concentrations compared with birth-assigned girls.\textsuperscript{18,20} Patient with coexisting hypogonadism and GH deficiency will not have a pubertal growth spurt when GH alone is replaced, as sex steroids stimulate GH as well as IGF-1 and have direct effects on the epiphyseal plate.\textsuperscript{18} Thus, GH and sex steroids are necessary for a normal pubertal growth spurt.\textsuperscript{18}

Clinicians caring for TGD youth may note that the pubertal growth begins with the onset of breast budding (e.g., Tanner stage 2 breast) in birth-assigned females, while in birth-assigned boys, this occurs in the later stages of puberty (e.g., Tanner stage 4 genitalia).\textsuperscript{16,21,22} There is sexual dimorphism in the increase in GH secretion that accounts for at least some of the height differentials between adult birth-assigned males and females associated with these pubertal stages.\textsuperscript{19,23} The pubertal growth spurt contributes to approximately 17% of final adult height, equating to 27.5–29 cm in birth-assigned girls and 30–31 cm in birth-assigned boys.\textsuperscript{1} In the absence of receiving GnRHa for gender dysphoria, birth-assigned males are on average 13 centimeters taller compared with birth-assigned females.\textsuperscript{1} It is thought that this height differential is from a combination of factors (Figure 1). The first is timing; birth-assigned females reach the peak height velocity on average two years earlier than birth-assigned males (11.5 and 13.5 years, respectively). This allows for more time for gain in height before puberty. Second, birth-assigned males reach a greater peak height velocity of approximately 9.5 cm/year, compared with 8.3 cm/year in birth-assigned girls.\textsuperscript{1,24,25}

Bone growth continues to occur while the epiphyseal plate remains cartilaginous; linear growth ends when the entire bone has ossified as a result of the process of senescence of the chondrocytes.\textsuperscript{18,28} This is thought to occur when the chondrocytes in the proliferative zone experience an accumulation of estrogen exposure and eventually become replaced with osteocytes.\textsuperscript{27} Clinically, observations from case reports of individuals with estrogen receptor defects or aromatase deficiency demonstrate very delayed epiphyseal closure and associated tall stature.\textsuperscript{28} No published studies have fully characterized the impact of final adult height or current height in an actively growing TGD youth and its impact on their gender dysphoria or lived experience.

4 | ASSESSMENT OF ANTHROPOMETRIC MEASUREMENTS IN TGD YOUTH

Assessment of a TGD youth’s anthropometric parameters is a component of the physical examination and should be approached in a sensitive, gender-affirmative manner. Methods to achieve accuracy and precision of growth measurements may be undervalued by clinicians, yet are of paramount importance. Assessment of height is best carried out by the use of a wall-mounted stadiometer when feasible.\textsuperscript{29} Currently, there is no research or clinical practice guidelines to support whether the birth-assigned or affirmed gender’s growth charts should be used for the assessment of growth and development.\textsuperscript{30} Additionally, baseline anthropometric parameters appear to be similar to population-based normative data, while some gender-diverse cohorts have reported increased rates of obesity.\textsuperscript{31,32} For children over the age of 2 years, it is currently recommended that children are evaluated using the Center for Disease Control charts for weight, height, and body mass index (BMI) from
the age of 2–20 years. The lack of research to guide the utilization of the birth-assigned vs. affirmed sex growth charts, which may alter the assessment of changes in anthropometric parameters, is challenging. This may also be complicated by interpretation of any changes in weight or BMI percentile in the setting of a concomitant eating disorder or disordered eating behavior, which is an associated comorbidity of gender dysphoria. Kidd et al. have proposed the interpretation of growth within both gendered growth charts and consideration for the prior patient history, pubertal stage, and any gender-affirming pharmacological interventions that may alter weight and height. The authors suggest continuing to use the birth-assigned growth chart during GnRHa therapy until gender-affirming hormones are implemented based on the underlying physiology. Specifically, TGD youth can be regarded as hypogonadal youth who would be expected to display a growth pattern similar to cis-gender peers with constitutional delay of growth and development until they begin gender-affirming hormones, at which time it may be most appropriate to use the affirmed-sex growth chart or use of both gendered growth charts.

5 | METHODS TO PREDICT FINAL ADULT HEIGHT IN TGD YOUTH

No published literature provides guidance on how to best predict the final adult height for TGD youth receiving GnRHa and gender-affirming hormonal treatment. Without medical intervention, adult height may be estimated using the corrected mid-parental target height, which is commonly determined by the Tanner method, derived by taking an average of the parents’ heights (after adjusting for a 6.5 cm addition for birth-assigned males or reduction for birth-assigned females). For example, a mother who is 160 cm and a father who is 180 cm would be expected to have birth-assigned female child who attained an average adult height of 163.5 cm or a birth-assigned male child who attained an average adult height of 176.5 cm. As visible by a comparison of siblings of the same birth-assigned sex, variations in height are common, and these predictions fall within ±10 cm (approximately 1.5 standard deviations) of the predicted height. In TGD youth, the effects of the intersection of puberty-suppressing medications and gender-affirming hormones in influencing a final adult height closer to the birth-assigned or affirmed gender have not been fully studied. In our experience, we have found that the height of transgender female adolescents who received GnRHa in early puberty followed by exogenous estradiol therapy attained a final adult height shorter than their birth-assigned (e.g., male) prediction, but taller than their affirmed sex (e.g., female) prediction.

Another tool commonly used for height prediction by pediatric endocrinologists is the determination of skeletal, or bone, age from a left-hand radiograph. The determination of skeletal age is performed by comparing with age-matched and sex-matched standards, most commonly using the Greulich and Pyle atlas. There are several methods to predict adult height, such as the Bayley-Pinneau method, based on this skeletal age, but in general, this lacks applicability to many people, as the standards are based on Caucasian children. Applying these prediction methods to an adolescent who is in the process of medical transition is not studied, especially in light that pubertal suppression leads to delays in skeletal maturation, gender-affirming hormones are being implemented in age ranges (e.g., 14–16 years) that would be consistent with delayed puberty in cis-gender peers and the unknown influence of gender-affirming hormones on final height predictions.

6 | USE OF GnRHa IN FOR PUBERTAL SUPPRESSION IN GENDER DYSPHORIA

GnRH analogues (GnRHa) are class of medications that lead to reversible pubertal suppression and are standard of care in TGD youth who meet strict diagnostic criteria. GnRHa are synthetic derivatives

![Figure 2](image-url)  
**Figure 2**  
Serum LH levels in response to GnRHa therapy. Prior to medical transition, LH exhibits pulsatile secretion in response to its upstream stimulator, GnRH. With treatment with GnRHa, LH levels initially increase during a “flare-up” followed by a “desensitization” phase leading to gonadotrope suppression and loss of LH pulsatility. Adapted from Ref. 42. LH, Luteinizing Hormone; GnRH, Gonadotropin-releasing hormone; GnRHa, Gonadotropin-releasing hormone Analog
of the native GnRH decapeptide, which differ predominantly via substitution of the 6th amino acid (glycine), which leads to greater potency and prolonged half-life compared with native GnRH. GnRHa initially acts as a "super-agonist" causing a transient "flare-up" phase during which time, the gonadotropins, LH and FSH, and downstream sex steroids increase. This initial phase is followed by subsequent reduction of gonadotropins and therefore, sex steroids, through desensitization of gonadotropes in the pituitary gland (Figure 2). In pediatrics, there is extensive clinical experience by pediatric endocrinologists in the implementation of GnRHa since the 1980s for central precocious puberty (CPP).44 When TGD youth meet eligibility criteria for GnRHa as established by current clinical practice guidelines, implementation of pubertal suppression can be considered when youth develop Tanner stage 2 (e.g., initial breast budding in birth-assigned females, testicular volume ≥4 ml in birth-assigned males) of puberty or later. However, the utilization of GnRHa remains an off-label use of medication, as currently there is no FDA-approved indication for gender dysphoria. Use of GnRHa agonist in youth with gender diversity, previously classified as gender identity disorder, was first implemented in the Netherlands in one of the oldest and largest pediatric transgender health programs. Known informally as "the Dutch protocol," this involved the use of GnRHa at Tanner stage 2 of puberty followed by subsequent consideration for gender-affirming hormones (e.g., exogenous estradiol or testosterone) at 16 years of age and gender-affirming surgeries after 18 years of age if desired by the patient. This was then adopted by pediatric transgender health programs in the United States. Psychological outcome data when this initial cohort was analyzed between the ages of 20 and 22 years demonstrated that transgender young adults who had been treated with GnRHa at the onset of pubertal development, as well as gender-affirming hormones and gender-affirming surgery, had similar psychological outcomes compared with population-based normative data.

GnRHa formulations include intranasal, intramuscular, and subcutaneous injectables of various duration, as well as subcutaneous implants. In gender dysphoric youth, most clinical experience includes injectable and subcutaneous implants. Injectable forms of GnRHa (e.g., leuprolide acetate and triptorelin) are also available as 1-, 3-, and 6-month formulations, which require careful timing of follow-up injections to maintain pubertal suppression and monitoring for development of the rare side effect of sterile abscesses. Histrelin acetate implants (e.g., Supprelin LA) are also commonly prescribed for their long duration of action, as well as for their efficacy; however, they require that a small incision be made in the subcutaneous tissue, typically of the upper arm, and may also be cost-prohibitive. More cost-effective histrelin acetate 50 mg subcutaneous implants, such as Vantus, which deliver 50 mcg/day, may be alternatives to Supprelin LA, which delivers 65 mcg/day, and are likely to be equally effective in TGD youth. Of note, the brand Supprelin LA has a pediatric indication for precocious puberty, while Vantas does not have; however, in the United States, Supprelin LA currently costs approximately $42,873, while Vantas costs significantly less at approximately $5,098. The use of a histrelin acetate implant is approved for one year; however, clinical experience from CPP demonstrates a longer duration of action of two years. These authors also have clinical experience with TGD patients lost to follow-up with histrelin implants still effective at 3–4 years.

7 | IMPACT OF GnRHa ON LINEAR GROWTH AND FINAL ADULT HEIGHT IN TGD YOUTH

A reduction in height velocity during GnRHa therapy in an actively growing child to a prepubertal growth velocity is an expected side effect in medical transition and has been shown to also lead to a reduction in height standard deviation score (SDS). GnRHa has been used in some instances as a treatment for short stature, when used in conjunction with GH therapy, in cis-gender children to lead to a taller adult height. As birth-assigned males are taller than birth-assigned females, current or final height could impact the experience of the gender diverse population to live in their affirmed gender, for example, a transmasculine adult with a low-normal height of cis-gender females has a very low height for cis-gender men. Within the gender-diverse community, some individuals describe themselves as having "height dysphoria" and in some instances could be severe enough to meet criteria within the diagnosis of body dysmorphism, although this has not been formally described in the research literature. Additionally, how this correlates with actual height has not been described. No studies have evaluated the impact of current or final adult height on gender dysphoria, nor characterized the heights of gender-diverse adults compared with cis-gender identified peers.

Several measures have been created to assess body image in the TGD population. Height and stature are included as a component to the Body Image Scale (BIS) created by Lindgren and Pauly in the as part of a 30-element scale of body dissatisfaction. Sub-analysis typically includes height as a “neutral” characteristic that is described by the authors as “hormonally unresponsive” compared with traits like genitalia or analyzed by body image subscale for masculinity and posture, and height is not commonly reported as an individual variable. Transgender men have been shown to have statistically higher rates of body dissatisfaction with their height.
compared with transgender women; however, transgender men have also been reported to have satisfaction with their height.66,68

BIS data from the Netherlands cohort showed that in 70 TGD youth aged 12-16 years, GnRHa therapy alone did not impact body dissatisfaction; however, this was assessed after only one-year duration.59 A follow-up study by the same authors of 55 young TGD adults who had been treated using GnRH agonist, including leuprolide and histrelin acetate.45,46 demonstrated that transfeminine youth had significantly higher rates of body dissatisfaction compared with transmasculine youth prior to receiving GnRHa.70 None of these studies have reported specifically the ratings of body dissatisfaction of height in TGD youth.

8 | IMPACT OF GnRHa ON WEIGHT AND METABOLIC PROFILE OF TGD YOUTH

Counseling related to changes in weight and need for lifestyle modification should be approached in a thoughtful manner, especially as TGD youth are at an increased risk for disordered eating and body dissatisfaction.34 Weight gain is listed as a common side effect of GnRH agonist, including leuprolide and histrelin acetate.45,46 Assessment of weight in children with CPP treated with GnRHa agonist has demonstrated mixed results and in some groups, weight gain appears to be transient.57,71-74 Yang et al. found a differential response in changes in BMI in CPP, with the baseline normal-weight birth-assigned females showing a significant increase in BMI-standard deviation-score (SDS) in comparison with the group that was overweight at baseline that did not; however, this has been supported other studies.72,73

Anthropometric response to GnRHa treatment in gender dysphoria warrants specific scientific investigation, as intervening in the underlying biology of CPP may not mimic the biology of classically timed puberty treated in gender dysphoria. A small study of 11 TGD youth followed on GnRHa for two years or longer demonstrated an increase in fat mass percentage and decrease in lean body mass percentage.67 Klink et al. reported no change in BMI SDS between GnRHa and beginning gender-affirming hormones in 34 TGD youth aged 11-18 years.41 Similarly, Schagen et al.’s cohort of 128 TGD adolescent reported no change in the BMI SDS one year after receiving GnRHa therapy in birth-assigned males, but birth-assigned females did demonstrate a statistically significant increase in BMI SDS during this time.58 Both of these studies included patients who were predominantly late to post-pubertal with a median Tanner stage 4 breast development in birth-assigned females and median Tanner stage 4–5 genitalia in birth-assigned males. Additionally, a recent study of 71 adolescent transgender females and 121 transgender males found that absolute BMI significantly increased during treatment with GnRHa alone; BMI SDS was not reported.75 Research studies are needed to understand if any changes in weight gain are transient or of longer duration, especially as it may impact metabolic health. Lower HDL-C levels as compared with NHANES controls have been observed and decreased insulin sensitivity has been reported as well in TGD youth.31,76

9 | SPECIAL CONSIDERATION FOR PROLONGED GnRHa USE IN NON-BINARY YOUTH

Future research is also needed to evaluate the outcomes specifically of non-binary identified youth who may desire GnRHa without desire to also progress to gender-affirming hormones. Newer publications have begun characterizing the mental health and medical outcomes of non-binary adults, but even fewer studies have described non-binary youth.77 Non-binary youth experience less access to health care than binary transgender youth.78 Outcome data on non-binary youth treated with prolonged pubertal suppression are needed. Current clinical practice guidelines do not provide guidance for medical providers and should be discussed within the ethical framework of balancing autonomy, benefits, and risks as well as exploring alternative medical options.78,79 From a growth perspective, prolonged suppression by GnRHa has the potential result in a taller-than-expected adult height, extrapolated from growth trends from adults with untreated hypogonadism that begins before epiphyseal closure.80

10 | ALTERNATIVES TO GnRHa FOR PUBERTAL SUPPRESSION

Administration of GnRHa for TGD with gender dysphoria may vary based on local availability, comfort level of the medical provider, cost and/or insurance coverage.53,81,82 Before the availability of GnRHa, progestins such as medroxyprogesterone or cyproterone acetate, depending on the geographical location of clinical practice, were the mainstay of therapy for children with CPP.83-85 The use of depot or oral medroxyprogesterone can be considered, especially in settings where GnRH agonist is too costly or not available; however, GnRH agonist should be utilized as first-line therapy when possible due to better efficacy and an improved side effect profile.3,86 The anti-androgen, cyproterone acetate, available outside of the United States, has been widely used in adult transwoman to suppress endogenous androgens and there is some experience reported in adolescents, although effects on growth velocity were not studied.3,87,88 A small but statistically significant reduction in height SDS has been reported in 21 transgender adolescent girls treated with cyproterone acetate, while no significant reduction was noted in 44 transgender adolescent boys treated with the progestin, lynesterol, for pubertal suppression. However, this is most likely related to mean age at progestin initiation of 17.1 years in transgender girls and 16.1 years in transgender boys in this study, when most linear growth has already been attained.88 Therefore, the effects of
progestins on growth velocity are not well-characterized. Combined oral contraceptives, which contain supraphysiologic dose of ethinyl estradiol, should not be used for HPG suppression in actively growing child, as estradiol fuses the epiphyseal cartilage. 89

11 | INFLUENCE OF GENDER-AFFIRMING HORMONES ON GROWTH

Current dosing protocols for pubertal induction for gender-affirming estradiol and testosterone administration are predominantly derived from experience with cis-gender hypogonadal patients and initial studies in adolescents support its safety. 3,90-94 Pediatric endocrinologists previously manipulated height in cis-gender girls through administration of high-dose estrogen to attenuate adult height by accelerating epiphyseal fusion. 95-97 While this practice has fallen out of favor, this approach may still be practiced by some pediatric endocrinologists when desired by parents of children with severe intellectual disability. 78 One case series of 11 transgender girls described an average adult height reduction of 4.3 cm in the setting of receiving a maximum dose of 6 mg of oral 17-beta estradiol or 200 mcg of oral ethinyl estradiol, but adult height was still above average for Dutch females. The authors concluded that if height attenuation is desired, exogenous estradiol should be used at higher doses and prior to the age of 16 years. 99 Another case series of transgender girls using similar doses of exogenous estradiol noted that only one of six subjects had a perceived adult height reduction; however, the authors acknowledge a variation in dosage paradigms and bone age at initiation of estradiol therapy, which may have impacted their results. 94 While 17-beta estradiol is now preferred to ethinyl estradiol for reasons of more favorable thromboembolic profile, transdermal 17-beta estradiol has been associated with an increase in IGF-1 levels in some studies compared with oral 17-beta estradiol; however, no randomized control studies have compared the adult height of transgender girls based on route of administration. 100,101

Finally, short stature has been treated by some pediatric endocrinologists using aromatase inhibitors that prevent the conversion of testosterone to estradiol and therefore should prolong the growth potential of the chondrocytes in the epiphyseal plate. 102-106 This method has been an approach to optimize height in cis-gender boys. The use of non-aromatizable androgens, such as the use of the use of dihydrotestosterone in cis-gender boys and oxandrolone in girls with Turner syndrome, has been found to increase height without advancing the bone age. 107,108 Oxandrolone has been previously suggested by current clinical practice guidelines to be a therapeutic option in short transmasculine youth. 7 A recent publication suggests that oxandrolone use in transmasculine adolescents may lead to small gains in adult height compared with mid-parental target height. However, this study was confounded by some patients within subgroups also receiving GnRH agonist therapy. 109 Nonetheless, oxandrolone may be a potential future therapy in youth 10 years and older to minimize the risk of dose-dependent virilization and potential risk for bone age advancement in younger children. 110,111

12 | FUTURE DIRECTIONS

Many questions remain unanswered in understanding how best to assess growth and use of height prediction tools in TGD youth, as well as the influences of timing, route of administration, and duration of puberty-suppressing medications and gender-affirming hormones on final adult height. In gender-diverse youth, the combination of some endogenous hormone exposure before GnRH agonist therapy with delayed implementation of gender-affirming hormones, compared with continuous endogenous hormone exposure in cis-gender peers, may potentially result in sub-optimally timed sex steroid exposure, potentially affecting chondrocyte senescence and negatively impacting adult height. Future therapeutic tools that could be innovative in TGD care include the potential use of other alternatives to GnRHa such as GnRH antagonists or other prostogens, such as depot medroxyprogesterone, the synthetic steroid danazol or the anti-androgen bicalutamide. 106,108 Regardless, as clinicians continue to provide patient-centered care, a discussion of the youth’s growth, including adult height prediction, and exploration of any family-based values around height and how this may influence their gender dysphoria should be included as part of their comprehensive care.

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AUTHORS’ CONTRIBUTIONS

Drs. Roberts and Carswell contributed equally as they conceptualized the content of this review article, drafted the manuscript, and edited and reviewed the final manuscript.

ORCID

Stephanie A. Roberts https://orcid.org/0000-0002-2811-1322
Jeremi M. Carswell https://orcid.org/0000-0003-3124-1344

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