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Puberty Assessment and Consideration of Gonadotropin-Releasing Hormone Agonists in Transgender and Gender Diverse Youth

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Abstract

Transgender and gender diverse (TGD) youth may pursue gender-affirming medical therapy in the form of gonadotropin-releasing hormone analogues (GnRHa), or "puberty blockers," if pubertal changes result in development or worsening of gender dysphoria. GnRHa monotherapy can allow TGD youth to explore gender without the distress of unwanted secondary sexual characteristics. However, given the potential effects of GnRHa on growth, skeletal development, neurodevelopment, fertility, and future surgical outcomes, it is critical to accurately assess pubertal status to facilitate fully informed conversations with TGD youth and families about risks, benefits, and unknown consequences of GnRHa monotherapy. The focus of this discussion will be on the approach to puberty assessment in TGD youth as well as the different effects of GnRHa monotherapy that may be important to TGD youth and their families.

Introduction

Clinical practice guidelines[1,2] suggest consideration of gender-affirming medical therapy in transgender and gender diverse (TGD) youth who experience worsening gender dysphoria with puberty, to allow for exploration of gender without further development of undesired secondary sexual characteristics. Gonadotropin-releasing hormone analogues (GnRHa) can be administered as monotherapy or in conjunction with gender-affirming hormone therapy (GAHT) with estradiol or testosterone, depending on the age and stage of puberty as well as the patient and family readiness for each type of potential medical intervention. This discussion will cover pubertal assessment of youth without differences in sex development, and considerations associated with GnRHa monotherapy of TGD youth in relation to pubertal stages.

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Pubertal Assessment

Generally, physical examination is the optimal approach to determining whether puberty has commenced, as pubertal levels of gonadotropins and sex hormones may be difficult to capture in early puberty. Genetic factors determine between 50–80% of pubertal timing,[3,4] so family history of puberty timing should be obtained, if possible, to guide anticipatory counseling of pre-pubertal TGD youth. Given the sensitive nature of the pubertal assessment, which can cause significant distress in TGD youth with dysphoria associated with pubertal changes, clear explanations about the examination and reasoning for why it is important to perform may help relieve anxiety. It may take more than one visit to build rapport with TGD youth before they feel comfortable with a pubertal assessment, and it may be helpful to ask whether youth have terminology they wish to use in relation to certain body parts. For example, more neutral terminology of “chest” tissue may be preferred over “breast” tissue. In children born with ovaries designated female at birth (DFAB), the examination will focus on visualization and palpation of the chest/breast tissue. In children born with testes designated male at birth (DMAB), the examination will focus on visualization and palpation of the testicles.

It is important to distinguish puberty from the parallel process of adrenarche and pubarche, which result from the activation of androgen release from the adrenal glands. Hallmarks of adrenarche and pubarche include the development of adult body odor, acne, axillary and pubic hair. While the timing of adrenarche can be quite similar to the timing of puberty onset, it can occur one to two years before or after gonadal activation.[4,5] For pre-pubertal TGD youth, the discussion about adrenarche or pubarche versus puberty may help to allay concerns if adrenarche occurs before pubertal onset.

In children with ovaries, the typical timing for onset of puberty is between eight to 13 years old, with overall trends toward younger ages and variation depending on body mass index, race, and ethnicity. In these youth, sexual maturity rating (SMR) or Tanner staging[6] should be based on thelarche and breast development. SMR stage 1 describes the pre-pubertal state with no breast development, and SMR stage 5 describes the adult mature stage of breast development. The first signs of puberty in designated female at birth youth occurs with SMR stage 2 of puberty, when breast buds develop just under the nipple. The firm rubbery tissue should be palpable and distinct from the surrounding adipose tissue, and often can feel tender upon palpation. SMR stage 3 of puberty is marked by the expansion of glandular breast tissue beyond the areolae, followed by the distinct secondary mound of the areola and papilla that appears over the primary mound of breast tissue in SMR stage 4 of puberty.[3,4] Menarche occurs on average 2.3 +/− 1.1 years after breast budding appears.[4]

In children with testes, the typical timing for onset of puberty is between nine to 14 years old. In these youth, SMR or Tanner staging should be based on testicular volume. SMR stage 1 is again the pre-pubertal state with no testicular enlargement or scrotal development, and SMR stage 5 of puberty describes the adult mature stage of testicular volume (20–25mL). SMR stage 2 is heralded by the thinning and stretching of the scrotal skin with reddening and increased rugation to accommodate enlarging testicles, as well as the growth of the testicular volume to 4mL (or longitudinal measurement >2.5cm). SMR stage 3 occurs

as the testicular volume increases to 8mL, and SMR stage 4 is reached with testicular volume increases to 15mL along with increased penis size and darkening of the scrotal skin.[3] From pubertal onset, it takes an average of 3.2 +/− 1.8 years to achieve adult testicular volume.[7]

Given the potential distress surrounding pubertal development in the TGD youth population, self-assessment or parental assessment of puberty may be a consideration if clinical assessment is not tolerated. While some studies have shown sub-optimal or mixed reliability, pubertal self-assessment could give clinicians a general idea of where TGD youth are in development. Factors that were associated with higher validity in children DFAB included normal body mass index (BMI), maternal assessment of breast development for those <11 years old, and self-assessment for those ≥ 11 years old.[8] Another study showed better agreement of self-assessed breast and testicular volume staging with clinical assessment if the youth were ≥ 10 years old.[9] Although self-assessment with orchidometer in one study of children DMAB only matched clinical assessment 36% of the time, the majority (95%) differed only by one size.[10] These studies have suggested that parental and child pubertal self-assessment could be sufficient to at least differentiate between pre-puberty and puberty if clinical assessment is absolutely refused.

Laboratory assessment can be obtained to confirm physical examination findings, but it can often be difficult to attain pubertal levels of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), and sex hormones, estradiol and testosterone, in the earliest stages of puberty. Patients should obtain labs fasting in the early morning for the best chance of capturing pubertal labs, as LH rises during sleep.[4] Ultrasensitive or pediatric LH and FSH measurement via immunoassay and ultrasensitive or pediatric estradiol and testosterone measurement via liquid chromatography and mass spectrometry or tandem mass spectrometry should be utilized when possible. Most laboratories provide typical reference ranges of gonadotropins and sex hormones for SMR stages, and a basal LH >0.2 mIU/L is generally accepted as consistent with the onset of puberty.[4] Laboratory studies should also be interpreted within the context of the physical examination, which takes precedent over the lab results if there are discordant results but clear pubertal changes on exam.

Determining an accurate puberty stage is critical to assisting with formulation of recommendations as well as adequate counseling about the risks and benefits of initiation of GnRHa and/or GAHT. In TGD youth who have not yet initiated puberty, the next steps will depend on how anxious the youth are about the puberty assessment exam or the onset of puberty, and if and when they wish to initiate GnRHa. Shared medical decision making should guide when the next pubertal assessment should be done, and TGD youth and their families should be counseled on the expected body changes to be alert for, such as tender breast buds or enlarging testicles, or sudden unexplained behavioral or mood changes, which may be signs that puberty has started.

Gonadotropin-releasing hormone analogues

GnRHa refers to both agonists and antagonists, which are potent inhibitors of gonadal estrogen and androgen synthesis. These therapies take advantage of the physiologic pulsatile

secretion of GnRH by the hypothalamus which stimulates release of gonadotropins, LH and FSH, by the anterior pituitary gland. In TGD youth, GnRH agonists are typically utilized to pause pubertal progression by abolishing the pulsatile GnRH signal to the pituitary gland. As such, initiation of GnRHa can result in an initial surge in gonadotropins and estradiol or testosterone until the pituitary gland recognizes the loss of pulsatile GnRH stimulus, typically by four weeks.[11] While generally thought of as a "reversible" intervention, GnRHa monotherapy can delay or interrupt important physiologic processes which need careful consideration. While guidelines suggest either ceasing GnRHa monotherapy or initiating GAHT by 16 years of age,[2] there may be compelling reasons to follow a more peer-concordant puberty timing model by ceasing GnRHa monotherapy or initiating GAHT by 14 years of age.[12]

Considerations of GnRHa in TGD Youth

Stage of Puberty and Potential Symptoms

Generally, once TGD youth reach late puberty (SMR stages 4–5) or are post-menarchal, GnRHa monotherapy will predictably result in significant hypogonadal symptoms such as hot flashes, fatigue or decreased energy, increased irritability, weight gain, sexual dysfunction, genitourinary symptoms, reduced libido, depressed mood, difficulty concentrating, difficulties sleeping, etc.[13],[14] Because of these symptoms, it may not be advisable to recommend GnRHa monotherapy, although initiation within one year of menarche could pause further breast development if TGD youth and family accept the potential negative side effects as detailed above.

Otherwise, menstrual suppression can be offered to post-menarchal TGD youth who have menses dysphoria[15] along with chest binding if chest dysphoria is also present.[16] For DMAB TGD youth who are in late puberty, hair removal[17] and voice training[18] could be adjunctive treatments to consider if they are still considering whether they desire estradiol-based GAHT, which would typically include both GnRHa or other androgen suppression along with estradiol therapy.

Growth

Another important consideration includes growth potential and timing of GnRHa in relation to the pubertal growth spurt, which is stimulated by estrogens in part due to their direct stimulation of growth hormone secretion as well as direct actions on chondrocytes at the growth plate.[19] Androgens also contribute to linear growth, mainly as a precursor to estrogen and conversion via aromatase but also likely through direct effects at the growth plate.[19] The pubertal growth spurt occurs earlier in estrogen-driven puberty than in testosterone-driven puberty, with peak height velocity occurring an average of 1.7 years after pubertal onset,[3] and corresponds most closely with SMR stage 2 to 3 of puberty.[20–22] In testosterone-driven puberty, peak height velocity has been demonstrated to occur an average of 2.0 years after pubertal onset, between SMR stages 3 and 4.[21,23] Ultimately, estrogen will slow linear growth by "aging" the growth plate which results in epiphyseal fusion.[19]

If there is evidence based on growth chart, or on pubertal assessment, that TGD youth are in the midst of their peak height velocity, counseling should include potential impacts on adult height attainment as this process could be interrupted by the introduction of GnRHa therapy,[24,25] although some recent literature indicate that there may not be a significant difference in attainment of target height with later addition of GAHT.[26,27]

Bone

A large portion of adult bone mass is attained during adolescence, driven by pubertal hormones. Peak bone mass, in turn, is a major determinant of future fracture risk. Therefore, the introduction of GnRHa monotherapy should be considered in the context of the dynamic skeletal developmental processes occurring in puberty. Bone mass accrual rate was noted to be highest at SMR stage 4 in one study,[28] and peak accrual was shown to occur within one year after peak height velocity, with plateau around four to seven years post-peak height velocity.[29]

Several studies have also demonstrated higher rates of low bone density for age in early pubertal TGD youth prior to any medical interventions.[30] Thus, TGD youth and families should be counseled about the expected slowing of bone accrual while on GnRHa monotherapy, and advised on adequate dietary calcium intake, vitamin D supplementation, and weight-bearing physical activities. Clinical practice guidelines advise monitoring bone mineral density by dual-energy X-ray absorptiometry, ideally with a baseline measurement to assess for any concerns prior to initiation of GnRHa.[2]

Brain

During puberty, brain structures develop further into sexually dimorphic regions with varying gray and white matter volumes depending on predominant sex hormone and stages of puberty.[31] Studies have described some differences in anatomical and functional MRI prior to gender-affirming medical therapy.[32,33] A small study did not demonstrate any concerning differences in executive functioning with GnRHa treatment.[34] As yet, there are no robust studies investigating the effects of GnRHa and/or GAHT on neurodevelopment in TGD youth, although studies are currently underway.

Fertility

While many TGD youth may not yet be thinking about family building at the outset of puberty, studies have shown that desire for fertility is important to TGD individuals although the majority do not access fertility preservation. At present, the effects of long-term GnRHa from early puberty onwards on future fertility potential remains unknown, so counseling in this regard is important.[35] Oocyte cryopreservation has been reported in a pre-menarchal TGD youth who remained on GnRHa,[36] and several more unpublished cases have been completed in the United States. Cryopreservation of immature gonadal tissue can be undertaken via research protocols developed for early puberty youth undergoing gonadotoxic chemotherapies, but these techniques can be invasive and are still experimental. Those who present in later puberty, post-menarchal or with SMR stage 4 to 5 testicular volume, may have the opportunity to cryopreserve gametes prior to initiating GnRHa and/or GAHT. In those who have progressed to SMR stages 4 to 5, there is an additional option to

stop gender-affirming medical therapy for several months in order to cryopreserve gametes should they decide to pursue fertility preservation later on.[35]

Insurance coverage and cost remain significant barriers to pursuing fertility preservation, but the conversation is an important one in terms of disclosing the unknown long-term effects of GnRHa and/or GAHT on future fertility potential.

Surgical

For TGD youth seeking future gender-affirming surgery, timing of GnRHa monotherapy to pubertal stage can affect surgical options and approach. For example, DMAB TGD youth seeking vaginoplasty may require intestinal tissue if GnRHa was initiated in earlier puberty (SMR stage 2–3), whereas those who are in later puberty (SMR stage 4–5) may be able to pursue penile inversion vaginoplasty.[37] In DFAB TGD youth, GnRHa monotherapy could eliminate the need for future mastectomy surgery if initiated early enough in puberty (SMR stage 2–3) for regression of tissue to occur. These issues should be discussed as part of the informed consent process reviewing risks and benefits of pursuit and timing of GnRHa therapy.

Discussion/Summary

Some TGD youth will experience significant or worsening gender dysphoria upon puberty, at which point they may consider proceeding with gender-affirming medical therapy with GnRHa monotherapy. Pubertal assessment of TGD youth can be challenging given the dysphoria around body changes related to puberty but is important to assess in order to adequately counsel TGD youth and their families about the implications of GnRHa therapy on various important developmental processes and to form thoughtful recommendations about medical options in the context of gender embodiment goals (i.e., stature, future vaginoplasty desire, fertility preferences, chest dysphoria, etc.). If absolutely necessary, parental and/or child pubertal self-assessment could be attempted if the goal is to simply distinguish between pre-puberty and puberty, at which point laboratory measurement of gonadotropins and sex hormones could confirm this assessment. As more data emerge in the many domains to consider with GnRHa monotherapy, it will be important to stay up-to-date with current research.

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