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Gender-Affirming Care of Transgender and Gender Diverse Youth: Current Concepts

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Introduction

Increasing numbers of transgender and gender diverse (TGD) youth (early pubertal through late adolescent) are seeking medical services to bring their physical sex characteristics into alignment with their gender identity—their inner sense of self as male or female or somewhere on the gender spectrum). While this is a relatively new field, close to 25 years of published research support current models of care. This review will focus on current concepts of TGD youth, impact of gender-affirming care, gaps in knowledge, challenges to care, and priorities for research.

Update on Prevalence and Terminology

The size of the TGD youth population is difficult to accurately discern. Survey-based studies estimate that the percentage of teenagers in the U.S. who identify as TGD ranges from 0.7% to 2.7%.(1–3). Clinics worldwide have reported on the growing number of TGD youth presenting for gender-affirming hormone treatment (GAHT) (4; 5). Terminology in this field is constantly evolving, with sex and gender as distinct entities. Sex is typically designated at birth, based on physical or chromosomal features, and may be male, female, or intersex. Gender identity exists separately on a spectrum that can be binary male or female, non-binary, gender fluid, or agender (6).

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Overview of Current Clinical Practice Guidelines for the Gender-affirming Model of Care

In recent years, a new model of care for TGD youth has emerged: the gender-affirming model. The basic premise is that every individual is entitled to live in the gender that is most authentic to them (7). Professional societies have published evidence-based guidelines encompassing care of TGD youth since 1998. The World Professional Association for Transgender Health (WPATH) is currently updating its 2012 Standards of Care 7 (8), and the Endocrine Society last updated its Clinical Practice Guideline in 2017 (9).

Following a thorough assessment by a qualified mental health gender specialist, TGD youth may be eligible for gender-affirming medical care after they have reached Tanner Stage 2 of puberty (6). Such treatment may include a reversible gonadotropin-releasing hormone agonist (GnRHa), or puberty blockers, to pause puberty, prevent otherwise permanent development of secondary sex characteristics that are not aligned with a person's affirmed gender identity, and allow time for further gender exploration. In adolescents > 14 years of age, there are currently no data to indicate whether pubertal blockers can be used as a monotherapy without potentially compromising bone mineral density (BMD). Older adolescents may request phenotypic transition with GAHT, either estradiol (in combination with an anti-androgen) or testosterone. While current clinical practice guidelines recommend initiation of GAHT in eligible adolescents once they have reached 16 years of age, the guidelines also recognize that there may be compelling reasons to initiate such treatment before age 16 in some adolescents, on a case-by-case basis (9). As with initiation of pubertal blockers, GAHT should only be initiated after a thorough assessment by a qualified mental health gender specialist. Detailed protocols for use of pubertal blockers (including alternatives to GnRH agonists) as well as for pubertal induction with GAHT, including guidelines for physical examination and laboratory surveillance, have been described (9).

Menstrual suppression is often desired by transmasculine and non-binary youth designated female at birth. Treatment options may include oral, injectable, intradermal, or intrauterine progestins and continuous combined oral contraceptives (10). For those TGD youth initiating testosterone, this treatment is generally effective in induction and maintenance of amenorrhea (10).

Outcomes of Current Models of Care

Mental Health

TGD youth have an increased prevalence of autism spectrum disorder and are also at increased risk for mood disorders, anxiety, depression, suicidal ideation, and suicide attempts (11–19). The frequency of internalizing disorders appears to be impacted by degree of family support: TGD youth with "very supportive" parents had a greater degree of positive self-esteem and life-satisfaction and a decreased frequency of depression and suicide attempts in comparison to those youth whose parents where "somewhat to not at all supportive" (20). Such findings underscore the concept that many of the mental health challenges faced by TGD youth are not intrinsic to their being transgender but rather likely

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reflect lack of societal acceptance. Notably, TGD youth presenting for gender-affirming medical care at earlier pubertal stages demonstrated better mental health and sense of well-being at baseline in comparison to older adolescents presenting at later pubertal stages, pointing to the potential benefits of gender-affirming medical treatment earlier in life (21; 22).

Only limited mental health outcomes data are available to support current clinical practice guidelines and standards of care for TGD youth. However, in recent years, a medium-term study (up to 6 years) and several shorter-term studies have demonstrated the positive and potentially life-saving impact of gender-affirming medical care for TGD youth (23–29). A prospective two-year study of 70 gender dysphoric adolescents in the Netherlands observed that treatment with a GnRH agonist/pubertal blocker was associated with a decrease in depression and an improvement in general mental health functioning (29). None of the 70 patients withdrew from this study, and all went on to treatment with gender-affirming sex hormones (29). After treatment with pubertal blockers, a 6-year follow-up study of 55 individuals from this original cohort reported on mental health outcomes after subsequent treatment with gender-affirming sex hormones and genital reassignment surgery (23). At the conclusion of this observation period, gender dysphoria was reported to have resolved, general psychological function improved, and, remarkably, sense of well-being was equivalent or superior to that seen in age-matched controls from the general population (23).

A number of subsequent reports have confirmed the positive mental health impact of gender-affirming medical care for TGD adolescents and young adults. In particular, a cross-sectional survey of more than 20,000 transgender adults (aged 18–36 years) found a significantly lower odds of life-time suicidal ideation (P=0.001) in those that had been treated with pubertal blockers during adolescence in comparison to those who wanted such treatment but did not receive it (24). Several shorter-term longitudinal studies have demonstrated that gender-affirming medical care was associated with improved body image, decreases in body dissatisfaction, and improved psychological functioning (25–28).

A 2020 survey of 11,914 transgender or nonbinary youth, aged 13–24 years, in which 14% of respondents were receiving GAHT, demonstrated that such treatment was associated a lower odds of recent depression and serious consideration of suicide compared to those who wanted such care but didn’t receive it (30). A separate survey study demonstrated that access to GAHT during adolescence was associated with lower odds of past-year suicidal ideation (P = 0.0007) compared to those who accessed such care during adulthood (31).

Physiological

Bone—Since 2015, when the first study examining the effects of GAHT on bone health in TGD adolescents showed low pre-treatment BMD by dual-energy X-ray absorptiometry (DXA) and impaired bone mass accrual in transgender women who initiated GnRHa in late puberty and were treated with more than five years of estradiol (32), additional studies have focused on the skeletal effects of gender-affirming medical therapy in TGD youth (32–35). These groups have shown lower BMD in transfeminine youth, with less concerning

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data in transmasculine youth (33–36). Because the studies were retrospective, no specific determinants of bone health were implicated for potential interventions.

A prospective study of early pubertal TGD youth in the United States about to begin treatment with a GnRHa demonstrated a greater prevalence of low baseline BMD in both those designated male and those designated female at birth, although the percentage of those with low BMD was higher in those designated male at birth (37). Prospective collection of dietary calcium intake, serum 25-hydroxyvitamin D, and physical activity assessments revealed globally low dietary calcium intake and that low physical activity was predictive of low BMD (37). Another recent study showed that TGD individuals have bone geometry trajectories matching gender curves if GnRHa was initiated in early puberty (38), suggesting that TGD individuals initiating treatment in early puberty have skeletal trajectories distinct from those initiating treatment in late puberty or adulthood. All studies to date have analyzed BMD Z-scores using sex designated at birth reference standards, and the International Society for Clinical Densitometry has not produced specific guidance on how to interpret DXA in TGD youth.

Growth—Early studies investigating height velocity, growth potential, and adult height attainment in TGD youth are still emerging, although variation in genetic height potential and pubertal stages at initiation of GAHT produces significant challenges to data interpretation (39). A study investigating growth in TGD youth during the first year of GnRHa treatment showed height velocity similar to pre-pubertal children except when GnRHa was initiated in later puberty (Tanner Stage 4), where height velocity was significantly below that seen in prepubertal youth (40).

Cardiometabolic Parameters and Lipids—Investigations on the effects of puberty suppression and GAHT on cardiometabolic parameters such as blood pressure, body composition, body mass index (BMI), and lipids in TGD youth are underway. In 36 transgender girls and 41 transgender boys at a median Tanner Stage 4 of pubertal development, one year of GnRHa increased fat percentage, decreased lean body mass percentage, and increased BMI (41). A small study of 9 transgender boys and 8 transgender girls were compared with age-, sex designated at birth-, and BMI-matched cisgender controls and found lower estimated insulin sensitivity and higher glycemic markers and body fat in TGD youth on GnRHa, but the study was of relatively short duration (42).

A cross-sectional study of older TGD adolescents (both designated males at birth and designated females at birth) on GAHT showed significant body composition differences compared with cisgender controls and higher insulin resistance in transfeminine youth when compared with cisgender male controls (43). A retrospective study of late pubertal transgender boys compared with BMI-matched cisgender girls revealed increased BMI and decreased high-density lipoprotein (HDL) in the transgender boys after starting testosterone therapy for a relatively short duration (<12 months) (44). Examination of a cohort of TGD young adults aged 22 years (71 transwomen and 121 transmen) treated with GnRHa and GAHT showed increased BMI as well as obesity prevalence of 9.9% in transwomen and 6.6% in transmen, compared with 2.2% ciswomen and 3.0% in cismen (45). Another study demonstrated pre-treatment HDL in TGD youth to be slightly lower when compared with

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age-matched controls but otherwise similar to age-matched National Health and Nutritional Examination Survey (NHANES) comparison group for BMI, blood pressure, and baseline laboratory measurements (46). Following treatment with GAHT, transgender girls have been shown to have increases in HDL and transgender boys to have decreases in HDL (47–49) – with differences influenced by presence of obesity (50).

Brain—Limited studies are currently available which evaluate the impact of gender-affirming medical care on neurocognitive development in TGD youth as recently reviewed (6). A small study from the Netherlands demonstrated no apparent adverse impact of GnRHa on the acquisition of "executive functioning," a developmental milestone typically achieved during puberty (51). A single case report demonstrated lack of expected white matter fractional anisotropy and a nine-point drop in operational memory after approximately 2 years of treatment with a GnRHa (52).

Other—A retrospective study 611 TGD adolescents who were 13–24 years old at initiation of GAHT for a median duration of 574 days of GAHT showed no incidental occurrence of arterial or venous thrombosis associated with GAHT (53). The expected rise in hemoglobin and hematocrit with testosterone therapy have been shown in TGD youth, with no significant adverse effects reported (34; 47; 49).

Surgical Care

In earlier years, gender-affirming surgeries had not been considered in TGD youth younger than the age of majority. Current clinical practice guidelines recommend delaying gender-affirming genital surgery until 18 years or older, with the WPATH SOC 7 additionally recommending one year of living in the affirmed gender (8; 9). In accordance with clinical practice guidelines, gender-affirming surgeons have performed chest masculinization surgeries at younger ages, where timing is based on physical and mental health status of the individual patient (8; 9; 54). A larger study of 68 transmasculine youth undergoing chest reconstruction surgery included patients 13–24 years, 33 of which were <18 years at the time of surgery (16 of which were ≤15 years), compared with 68 transmasculine youth who did not undergo surgery showed a significant improvement in chest dysphoria in the postsurgical group (55). A smaller study of 14 TGD youth ranging in age from 13.4–19.7 years who pursued chest reconstructive surgery reported high satisfaction rates with no regret and minor surgical complications of keloid, seroma, and hematoma in five individuals (56). More recently, surgeons have performed vaginoplasty surgeries on TGD youth under 18 years of age, on an individualized basis, with need to adjust surgical approach for those who initiated GnRHa in early puberty (57).

Fertility

A discussion about fertility preservation is an essential part of the evaluation of every TGD youth prior to initiation of either pubertal blockers or gender-affirming sex hormones. While late pubertal/post-pubertal adolescents are likely able to provide a sperm sample or undergo egg cryopreservation, TGD youth treated with GnRHa during early puberty are at increased risk for compromised fertility if they then proceed with transition with GAHT (6). An important advance in fertility preservation has been the demonstration of *in vivo* oocyte

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maturation in a gender dysphoric designated female at birth with a male gender identity who was treated with a GnRH agonist at Tanner stage 2, resulting in pubertal suppression who concurrently underwent a short course of ovarian stimulation with follitropin-alpha and human chorionic gonadotropin (58). *In vivo* maturation of sperm in a gender dysphoric designated male at birth with a female gender identity who was treated with a GnRHa at Tanner stage 2 has not yet been reported.

Gaps in knowledge and challenges to care

In addition to the need for long-term safety and efficacy studies to evaluate current clinical practice guidelines and standards of care, significant gaps in knowledge remain with respect to optimal management of TGD youth. For example, increasing numbers of youth identifying as gender-nonbinary are presenting for care, for whom no formal guidelines currently exist (59–65). In addition, a putative condition labeled “rapid-onset gender dysphoria” (ROGD) has been proposed to describe adolescents who first experience gender dysphoria either in the later stages of puberty or after puberty has been completed (66). However, significant methodological concerns have been raised calling into question the existence of ROGD, itself, including that only parents and none of the adolescents with gender dysphoria participated in the study, and that the parents were recruited from websites not thought to be supportive of transgender youth (67). Additional gaps in knowledge exist, in particular, with respect to the impact of GnRHa/pubertal blockers on fertility, skeletal health, and neurocognitive development, as recently described (6).

In addition to the above noted gaps in knowledge, there are significant challenges to care of TGD youth. All hormonal interventions for TGD youth are considered “off-label” and are often denied by insurance companies. Furthermore, lack of formalized training limits access to optimal care (68). Another notable challenge to care pertains to sexual anatomy: designated males at birth treated with a GnRHa in early puberty who subsequently transition with estrogen and request vaginoplasty after reaching the age of legal majority will likely require a more complex surgical procedure than that typically required for designated males at birth who request vaginoplasty after completing endogenous, testosterone-mediated puberty (69). Most notably, there are unprecedented challenges to the care of TGD youth, both in the U.S. and abroad, with policies and in some cases, state-based legislation banning gender-affirming medical care to TGD minors and criminalizing medical providers of such care (6). As noted in recent position statements sponsored by the Endocrine Society, Pediatric Endocrine Society, and the United States Professional Association for Transgender Health, these legislative efforts are thought to “lack scientific merit and in some cases misinterpret or distort available data” (70; 71).

Summary

Key advances in the care of TGD youth include the recognition that being transgender or gender diverse is not rare, and that it being TGD is no longer considered a mental illness, but rather represents an example of human diversity (6). Numerous studies, primarily of short and medium term duration (up to six years), demonstrate the clear beneficial—even

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life-saving mental health impact of gender-affirming medical care in TGD youth. Long-term safety and efficacy studies are needed to optimize medical care for TGD youth.

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